VOLUME 98 • JULY 1959 • NUMBER 1

DISEASES OF CHILDREN

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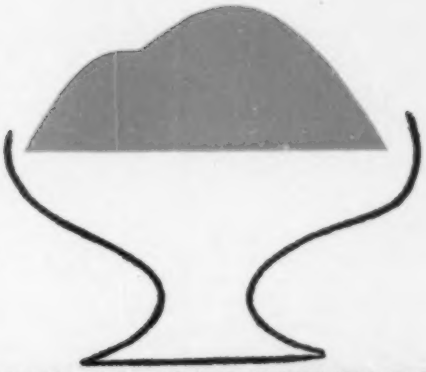

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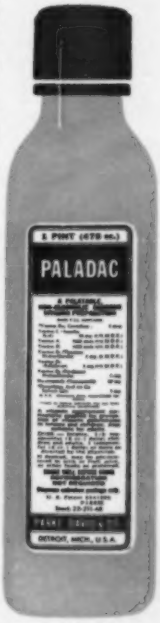

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1. Wiese, Hilda F., et al.: J. Nutrition 66: 345, 1958
2. Adam, Doris J. D., et al.: Ibid.: 555
3. Hansen, A. E., et al.: Ibid.: 565

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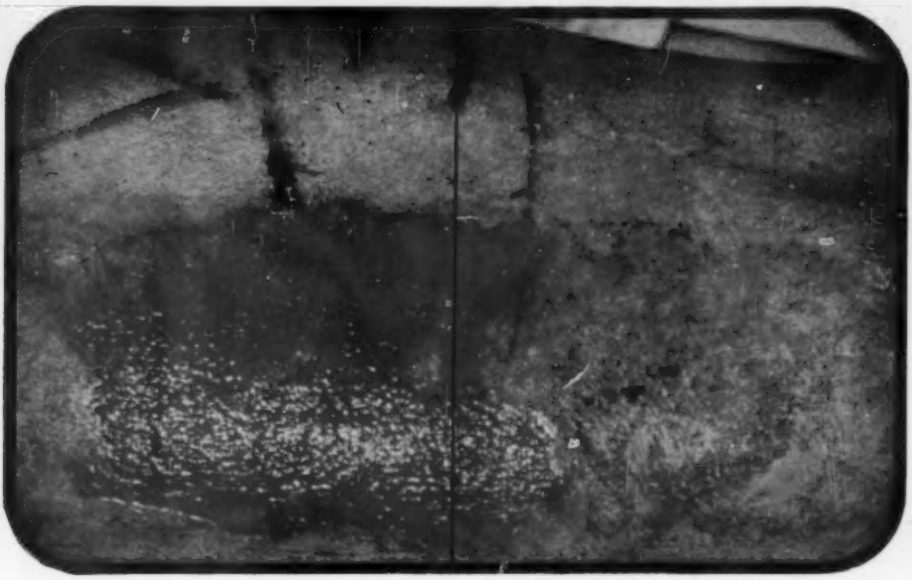

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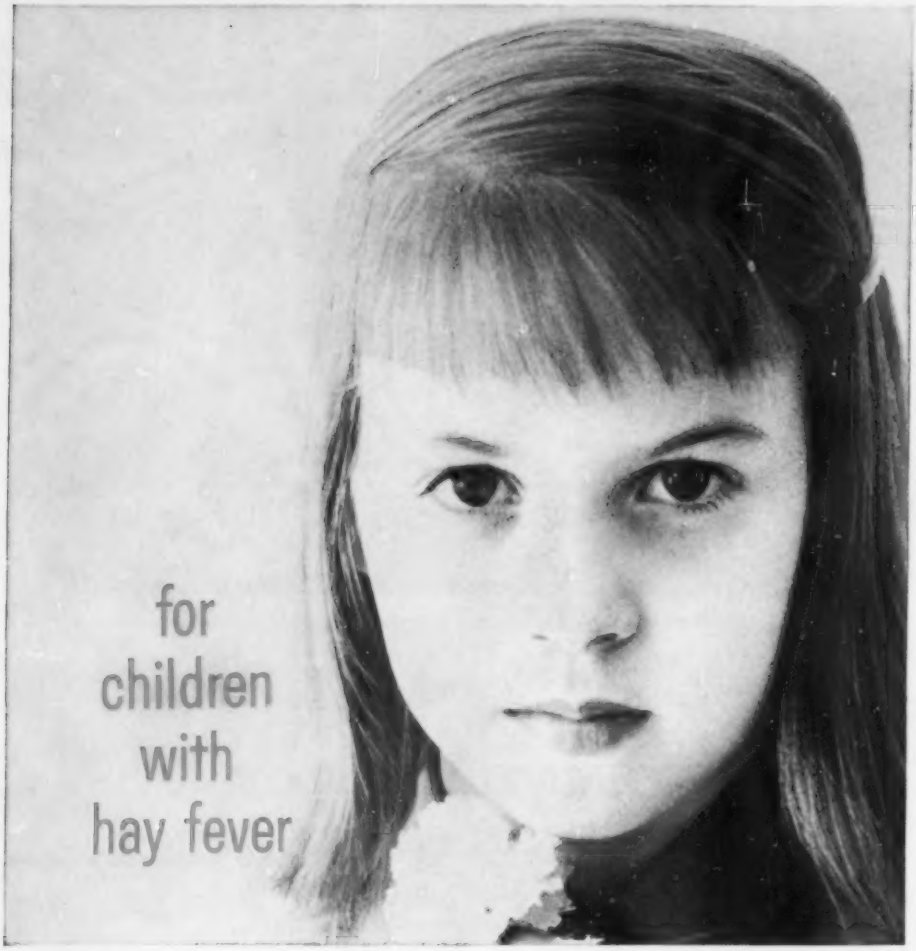

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DISEASES OF CHILDREN

Acceptance of a Soya Food by Infants

GEORGE R. BARNES Jr., M.D., Iowa City

From October, 1955, to May, 1957, an investigation of a new protein food for infants was undertaken. Because of the paucity of published information of attempts to evaluate the acceptance of infant solid foods, it was thought of interest to report such an appraisal. A soya bean preparation was selected for the study because of its potentiality as an economic source of protein of good quality for the feeding of infants. The excellent quality of the protein of soya bean has been well established for the feeding of animals.[1] Various preparations of this protein have been used widely for the feeding of infants with problems of an allergic nature. The purpose of the study was to ascertain the number of babies who would accept this new food, the length of time they would continue to take it, and the incidence of reactions to it. Additional studies, which will be reported separately, were performed to determine the biologic efficiency of the product.[2]

Nature of the Product

An extract of the soya bean was fortified, so that it was similar to animal protein.* It had the following composition: fat, 5.0%; water, 79.6%; carbohydrate (including crude fiber), 1.2%; protein, 14.2%. The following amounts of vitamins and amino acids were added to each 100 gm. of the food during its preparation: 120μg. thiamine hydrochloride, 280μg. riboflavin, 4,400μg. nicotinamide, 550μg. pyridoxine hydrochloride, 2.5μg. vitamin B_{12}, 280μg. DL-methionine, and 56μg. L-cysteine hydrochloride. The texture was that of a puréed food, the flavor bland, and the odor nut-like. It was packaged in small tins, each containing 105 gm.

The soya food was offered as a dietary supplement and not as a substitute for milk.

Subject Material

The subjects, 191 infants, ranging between 1 and 16 months of age, were selected from the following sources: Child Health Clinic (69, or 36%), the Private Clinic (82, or 43%), the Metabolism Ward of the University Hospitals, State University of Iowa (9, or 5%), and the private practice of two pediatricians† in Iowa City (31, or 16%). Infants cared for in the Child Health Clinic are children of undergraduate and graduate students of the State University of Iowa. The well babies seen as private patients at the University Hospitals are children of families living in Iowa City; many are children of house officers of the University Hospitals and of members of the senior staff of the medical school. The Metabolism Ward of the Department of Pediatrics provides for six to nine well babies as subjects for metabolic studies concerning various aspects of nutrition.[3]

The test group was unusual in relation to the greater than average educational background of the parents and the high percentage of parents

Submitted for publication Dec. 19, 1958.
Aided by a grant from Lever Brothers Company.
From the Department of Pediatrics, College of Medicine, State University of Iowa.
Present Address of Dr. Barnes: Department of Radiology, University Hospitals, Iowa City.

* The soybean food (LP-60) was prepared by Lever Brothers Company and is not commercially available.

† Drs. Lorraine Frost and John R. Maxwell cooperated in this study.

in various professional fields. For example, fathers of 20% of the subjects were physicians.

Procedure

Parents of infants being cared for in the clinics of the University Hospital were informed of the existence of the experimental baby food, and, if they were interested in attempting to feed it to their child, an initial supply of three cans was given to them. The majority of the parents received the food from one of three pediatricians. The physicians attempted to discuss the food briefly in the manner in which any new food might be discussed. The composition was generally not stated.

Because it was not considered necessary to test all of the infants for an extended period, an unlimited supply was not made available to all families. When adequate supplies were available, however, parents were able to obtain one carton (24 cans) at a time in the clinic.

Follow-up information was obtained at the time of return visits to the clinics or by telephone calls to the parents. A record was kept of the amounts of food obtained, the amounts taken daily, and the comments of the parents. After sufficient time had elapsed for an adequate trial of the food, a questionnaire was sent to each family to procure detailed information.‡ Ninety per cent of the families completed and returned the questionnaires.

‡ The questionnaire asked information regarding the following: number of children in the family; incidence of allergies; details of feeding history; incidence of bowel or skin difficulties; spitting up or vomiting before or during feeding of the soya bean food; details of feeding and response to the food; parents' reaction to the food; varied questions directed to parents of infants who rejected the food.

Iowa City is a small university community with a population of 28,000. Many of the families in the test group lived in housing areas in the immediate vicinity of the University Hospitals. These factors facilitated the collection of data.

The method of distribution of the soya bean preparation by the pediatricians not associated with the University Hospitals differed in some respects from that described above. Parents were acquainted with the composition of the food and given an initial supply of three cans. Additional supplies were limited to 24 cans. The same methods of gathering data as outlined previously were utilized.

Results

Observations were made concerning the number of infants who would accept the food, the length of time it would be accepted, and the incidence of unfavorable reactions. It was offered to 207 infants, of whom 16 have had to be excluded from the analysis because adequate follow-up information could not be obtained.

Factors Influencing the Acceptance and Rejection of the Experimental Food.—An infant who readily consumed at least three cans of the soya bean food and ate it consistently within a two-week period, was considered to have accepted the food. An infant who did not accept it readily within a period of two weeks was considered to have rejected the food. In the group of 191 infants ranging from 1 month to 16 months of age, 159 (83%) accepted it and 32 (17%) rejected it.

TABLE 1.—*Reception of Soya Bean Food According to Age of Infant When First Offered*

Age When First Offered (Month)	Total No.	Group, %	Acceptance		Rejection	
			No.	%	No.	%
1st	9	5	6	67	3	33
2d	33	17	29	88	4	12
3d	38	20	31	82	7	18
4th	40	21	33	83	7	17
5th	14	7	14	100	0	0
6th	18	11	16	89	2	11
7th	16	8	13	81	3	19
8th	9	5	9	100	0	0
9th	3	1	3	100	0	0
10th	3	1	1	33	2	67
11th and over	8	4	4	50	4	50
Total	191	100	159	83	32	17

TABLE 2.—*Reception of Soya Bean Food According to Source of Test Group*

Source	Acceptance		Rejection	
	No.	%	No.	%
Child Health Clinic	49	71	20	32
Private University Clinic	72	88	10	12
Metabolism Ward	9	100	0	0
Practice of Community Pediatricians	29	94	2	6

TABLE 3.—*Reception of Soya Bean Food According to Birth-Order of Subjects*

Birth Order	Subjects in Total Group		Acceptance		Rejection	
	No.	%	No.	%	No.	%
1st	91	48	69	76	22	24
2d	54	28	49	91	5	9
3d	26	14	23	88	3	12
4th or more	20	10	18	90	2	10
Total	191	100	159	83	32	17

Table 1 depicts the acceptance rate of the experimental food as related to the age of the infant at the time it was first offered. Of 32 infants who rejected the food, 9 were less than 1 month of age or older than 10 months. Thus, in these age groups, 45% of the infants (9 of 20) refused the food; whereas in the age group between 1 and 10 months, only 13% of the infants (23 of 171) refused it.

Thirty-seven babies received the experimental preparation as the first solid food. Thirty (81%) of these infants accepted it and seven (19%) rejected it. Nine received it as the only solid food for a period of four to seven and a half weeks.

Table 2 shows the percentage of acceptance and rejection of the food according to the source of the subject material.

Table 3 relates the acceptance and rejection of the experimental food to birth order of the test subjects.

Length of Time the Experimental Food Taken.—The babies who accepted the food consumed it for periods varying from several days to 12 months (quantities of one-fourth can to two cans per day). Table 4 presents information concerning the number of cans consumed. Of the 159 babies accepting the food, 115 (72%) consumed more than 24 cans. One of the subjects ate more than 300 cans.

There appeared to be no particular "fatigue factor" in the use of the product. Many babies vary periodically in their enthusiasm for specific foods; response to the soya bean food was not an exception to this general observation.

Unfavorable Reactions to the Experimental Food.—Two infants in the total group apparently exhibited evidence of intolerance to the food. One was a 6-month-old infant who was given it on only one occasion, and the mother suspected it to be the cause of vomiting and loose stools. This baby had a severe gastrointestinal allergy with inability to tolerate almost all solid foods and milk or milk substitutes, and was known not to tolerate soya bean formulae.

The second was a 5-month-old infant who readily consumed 24 cans, but an additional supply of the food was not requested by the mother because she thought it caused the baby to have loose bowel movements. The mother reported no similar problem with other foods, nor were there any obvious allergic manifestations in the infant. The mother had hay fever and a sibling had eczema.

A few minor side-effects were reported, none being of sufficient concern to the parents to suggest discontinuing the feeding of the experimental product. Four mothers reported that it made the babies' stools

TABLE 4.—*Total Amount Consumed by Infants Accepting Soya Bean Food*

No. of Cans	No. of Subjects	% of Total
3	4	2.5
4-7	4	2.5
8-10	4	2.5
11-24	32	20.1
25-48	67	42.1
49-72	20	12.6
73-96	11	7.0
97-144	9	5.7
More than 145	8	5
Total	159	100

firmer; five mothers stated that it caused the stools to become looser. Several recorded a stronger odor and a darker color to the bowel movements.

There was no increased incidence of spitting up or vomiting, loose stools, skin rash, perianal redness, or other reactions during the period of its ingestion. In answering the questionnaires, parents correlated a number of minor problems in the babies with ingestion of a variety of foods, including spinach, cereals, eggs, wheat, pears, bananas, orange juice, and all types of vegetables.

The relative absence of unfavorable reactions to the experimental product was not a reflection of an unusually small number of "allergic families" in the study group. According to reports written by parents on the questionnaire (admittedly a crude method of collecting data concerning allergy), there was no significant difference in the incidence of allergy in the families of the test group from that of the general population.

This study has shown that there was no direct correlation between a mother's dislike or distaste for the experimental product and the infant's acceptance. There were many parents who had strong negative reactions to the taste and odor of it, but these were equally distributed in the groups of acceptance and rejection.

Comment

There are no published data to show the percentage of acceptance for various infant foods and it is therefore impossible to compare the reception of the experimental food with that of other preparations. It would appear that the response (83% acceptance) to it was extremely favorable.

Beal [4] states that during the past 10 years there has been a definite tendency to introduce solid foods into the diet of infants at a progressively younger age. However, she reports that in spite of the earlier introduction of solid foods, there is a definite disparity between the offering and the acceptance, the latter often being delayed an appreciable length of time. She states that the average child does not willingly accept solid foods before the age of 2½ months. The results of our study would agree with those of Beal in respect to the high percentage of rejection of the test product and other foods in very young infants.

The Committee on Nutrition [5] of the American Academy of Pediatrics has concluded that there are no specific benefits derived from the introduction of solid foods into the diet of infants prior to 2½ to 3 months of age.

A large number of subjects rejecting the food were in the youngest or oldest age groups. These infants apparently were either not ready for solid foods or, in the older age group, were beginning to turn to the table for their diets. Six (19%) of the babies who refused it were at the same time refusing all or the majority of other solid foods.

Solid foods are routinely withheld from the diets of infants in the Metabolism Ward until the age of 6 months. The 100% acceptance rate of babies in the Metabolism Ward (Table 2) may indicate a favorable response to solid foods when offered at a favorable time and by experienced personnel.

The majority of the families included in this study were in a low-income group, since many of the fathers were graduate students and resident physicians. Thus, they might have been more willing, for economic reasons, to persist in feeding an experimental preparation which would be supplied without charge. This may have been a factor in the high acceptance rate of the food. On the other hand, a group containing many families of physicians and allied professions might be more skeptical about attempting a new and untried food. However, there was no significant difference in the reception of the soya bean product by the infants of physicians (33, or 85%, accepted the food and 6, or 15%, rejected it) from that of the total group.

Summary

The clinical evaluation of a new protein food for infants has been discussed with respect to its reception by infants and the incidence of reactions to it. Virtually no reactions occurred. It was readily accepted (83% of 191 infants). Infants did not appear to tire of it, generally continuing to accept it as long as they remained receptive to other baby foods.

I am indebted to Drs. Charles D. May and Samuel J. Fomon for their assistance in the planning of the study and preparation of the manuscript.

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The Adequacy of Soya Bean Protein in Promoting Nitrogen Retention in Infancy

Preliminary Study

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In previous study of normal infants fed pooled, pasteurized human milk ad libitum with additional vitamins (A, C, and D) but no other supplementary foods,[1] the mean daily intake of protein between 4½ and 6 months of age was found to be 1.7 gm. per kilogram (standard deviation ±0.3). It has long been customary to supply considerably greater intakes of protein to infants receiving formulae, on the reasonable assumption that too little protein was likely to be more detrimental to the infant than an excess; there is as yet no answer to the question of whether protein supplied from other sources may enable infants to thrive as well as does human milk.

The present study was designed to test the effect of supplying a significant proportion of the infant's intake of protein from another source while keeping the total intake of protein similar to that of infants reared on human milk. A protein food prepared from soya beans was chosen for this purpose. Studies of the acceptance of this food by infants had already been undertaken.[2]

According to the plan of the experiment, if poorer growth and less retention of nitrogen had resulted when a portion of the protein was derived from the soya bean, it could have been concluded that the requirement of protein from soya bean is greater than that for protein from human milk. In this case more demanding studies concerning equivalence of protein from these two sources would not have been warranted. On the other hand, failure to demonstrate a considerable difference in growth and retention of nitrogen by infants receiving the two feedings could not be taken to indicate that the protein of the soya bean is actually equivalent to the protein of human milk in these respects. A minor difference between the two proteins might not be detected by the procedure employed.

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Subjects

The subjects consisted of four normal infants, three boys and one girl (R. D.), between 121 and 256 days (approximately 4 and 8 months) of age. The infants were cared for in a previously described Metabolism Ward.[3] They remained well throughout the study; M. Ew. had had varicella shortly before the beginning of the present study (onset of rash at 158 days of age).

Three of the infants had received pooled, pasteurized human milk during the entire first 6 months of life when they served as subjects for other metabolic studies.[1] The other infant (R. D.) was studied while receiving boiled whole cow's milk without additional carbohydrate[4] until the age of 121 days; this infant then received pasteurized human milk until 149 days of age.

Procedure

The general plan of the experiments is provided in the Table. Solid foods were added to the diet of R. D. at about 5 months (149 days) of age and to the diets of the other infants at about 6 months (181 to 187 days) of age. The soya bean food was included among the first solid foods given to two of the infants (M. R. and R. D.) while the other two infants received only pears and bananas as the first solid foods. When necessary for maintaining the constancy of the intake of protein or calories, homogenized whole cow's milk and/or cream was given in addition to human milk.

Experimental Data from Subjects *

Subject	Age, Days	Daily Intake (Calculated) Energy, Cal/Kg.	CHO, Gm/Kg.	Fat, Gm/Kg.	Protein, Gm/Kg.	Wt. Gain, Gm/Day	Age, Days	Daily Balance of Nitrogen Weight, Gm.	Length, Cm.	Intake, Mg/Kg.	Excretion, Mg/Kg.	Retention, Mg/Kg.
M. Ew.	165-182	Diet: PHM † 1,100 ml.										
		94	9.5	5.6	1.42	—7.9 ‡	179	7,400	71.4	227	174	53
	183-195	Diet: PHM 600 ml., pears 105 gm., bananas 105 gm.										
		73	10.0	3.2	1.05	1.2	193	7,325	71.8	168	132	36
	196-210	Diet: PHM 1,000 ml., pears 60 gm., bananas 60 gm.										
		98	11.8	5.1	1.33	15.0	207	7,500	71.8	213	171	42
	211-227	Diet: PHM 450 ml., pears 90 gm., bananas 90 gm., soya bean food 36 gm., sugar 36 gm., 40% cream 55 gm.										
		80	7.6	4.9	1.39	25.7	221	7,950	72.0	223	140	83
							234	8,070	72.7	223	154	69
L. M.	141-186	Diet: PHM 1,100 ml.										
		93	9.8	5.3	1.40	17.8	148	7,610	66.3	230	177	53
							162	7,885	67.7	221	170	51
	187-214	Diet: PHM 600 ml., pears 105 gm., bananas 105 gm.										
		67	9.2	2.9	0.93	—4.6	197	7,980	70.0	140	141	—.91
							211	7,850	70.1	157	114	43
	215-228	Diet: PHM 1,100 ml., pears 60 gm., bananas 60 gm.										
		98	11.6	5.2	1.30	38.4	225	8,300	70.1	209	142	67
	229-248	Diet: PHM 500 ml., pears 100 gm., bananas 100 gm., soya bean food 40 gm., sucrose 40 gm., 40% cream 60 gm.										
		100	12.5	4.9	1.40	43.4	239	8,800	71.3	224	130	94
	249-256	Diet: PHM 300 ml., pears 100 gm., bananas 100 gm., soya bean food 40 gm., sucrose 10 gm., 40% cream 60 gm.										
		82	8.5	4.7	1.42	28.5	252	8,820	72.0	227	133	94
M. R.	139-160	Diet: PHM 1,020 ml.										
		94	9.8	5.3	1.73	23.5	149	7,450	65.8	277	191	86
	161-166	Diet: PHM 1,050 ml.										
		91	9.5	5.1	1.69	48.0	163	7,700	66.5	271	182	89
	167-180	Diet: PHM 1,140 ml.										
		95	9.9	5.4	1.66	30.7	177	8,300	66.7	266	196	70
	181-208	Diet: PHM 570 ml., pears 90 gm., bananas 60 gm., soya bean food 55 gm., 40% cream 65 gm.										
		88	7.4	5.6	1.88	17.7	191	8,400	68.4	306	225	81
							205	8,650	68.4	294	219	75
	209-227	Diet: PHM 600 ml., WCM † 250 ml., pears 90 gm., bananas 90 gm., 40% cream 30 gm.										
		86	9.1	4.7	1.79	33.3	219	9,150	68.4	286	213	73
	228-236	Diet: PHM 540 ml., WCM 225 ml., pears 81 gm., bananas 81 gm., 40% cream 27 gm.										
		74	7.7	4.1	1.54	25.0	233	9,450	69.9	246	175	71
R. D.	121-140	Diet: PHM 1,200 ml.										
		127	13.3	7.2	2.33	44.7	131	6,755	62.4	373	211	162
	141-148	Diet: PHM 1,140 ml.										
		109	11.2	6.1	2.24	—2.1	145	7,115	63.4	359	183	176
	149-154	Diet: PHM 570 ml., pears 90 gm., bananas 60 gm., soya bean food 55 gm., 40% cream 65 gm.										
		105	8.9	6.7	2.23	5.0						
	155-161	Diet: PHM 570 ml., pears 95 gm., bananas 65 gm., soya bean food 60 gm., 40% cream 65 gm.										
		104	8.9	6.6	2.25	20.8	159	7,225	63.8	360	269	91

*Experimental Data from Subjects**—Continued

Subject	Age, Days	Daily Intake (Calculated) Energy, Cal/Kg.	CHO, Gm/Kg.	Fat, Gm/Kg.	Protein, Gm/Kg.	Wt. Gain, Gm/Day	Age, Days	Daily Balance of Nitrogen Weight, Gm.	Length, Cm.	Intake, Mg/Kg.	Excretion, Mg/Kg.	Retention, Mg/Kg.
	162-176	Diet: PHM 600 ml., pears 95 gm., bananas 65 gm., soya bean food 60 gm., 40% cream 65 gm.										
		103	8.9	6.5	2.25	14.2	173	7,600	64.7	360	269	91
	177-197	Diet: PHM 600 ml., WCM 250 ml., pears 90 gm., bananas 90 gm., 40% cream 30 gm.										
		99	10.4	5.5	2.01	21.2	187	7,925	64.7	333	219	114
							194	7,950	66.7	310	234	76

* Each metabolic balance study was 72 hours in duration. Indicated age, weight and length refer to first day of balance study.
† PHM=pasteurized human milk; WCM=whole cow's milk.
‡ Failure to gain weight despite adequate intake may have been related to recent varicella (onset of rash at 158 days of age).

During those periods when the soya bean food was given, 41% to 45% of the total intake of nitrogen was derived from this source.

The attempt to maintain constant the intake of calories, carbohydrate, fat, and protein throughout the entire period of study was only partially successful. The amount of solid foods (low in content of protein) offered to two of the infants, M. Ew. and L. M., was at first so generous that ad libitum ingestion of pasteurized human milk was less than anticipated. This resulted in significantly less intake of total calories and protein (Table: M. Ew., 183 to 195 days of age; L. M., 187 to 214 days of age) than in the previous control period when only human milk was fed. Therefore, the amount of solid food offered to these infants was decreased with resultant greater intake of milk.

Materials

Pears and bananas employed in the study were prepared commercially and supplied in cans, the same lot being used throughout the study.

The food used as the source of soya bean protein was an experimental product, LP-60,* enriched with 280 mg. of DL-methionine and 56 mg. of L-cysteine per 100 gm. The final content of protein and amino acids was 14.2 gm. per 100 gm. of the food. More detailed record of the composition of the food has been presented elsewhere.[3]

The quantity of each solid food was weighed to the nearest 1 gm.; none of the solid food offered to the infants was refused during a balance study.

Methods

In the Table the approximate daily intake of protein was calculated from the determined intake of nitrogen by multiplication with the factor 6.25. Daily intakes of carbohydrate and fat in human milk and cow's milk were calculated from tables of composition of foods.[6] The manufacturer's analysis was accepted for the content of carbohydrate and fat in strained fruits and in the soya bean food. Caloric content of the various foods was calculated from the content of carbohydrate, fat, and protein.

Collection procedures and analytic methods were similar to those reported previously.[5] Homogenates of solid foods were prepared in a manner similar to that described for feces.

Results

Growth.—The loss of weight by Subject M. Ew. between the ages of 165 and 182 days (Table) may have been related to the recent occurrence of varicella. Fever and looseness of stools with loss of weight had occurred before the appearance of the varicella eruption at 158 days of age.

During the periods when large amounts of solid foods (low in content of protein) were given, M. Ew. (183 to 195 days of age) gained poorly and L. M. (187 to 214 days of age) lost weight. The daily intakes of the two infants during these periods were approximately 73 and 67 Cal. per kilogram, and 1.05 and 0.93 gm. of protein per kilogram, respectively. Similarly, during a 7-day interval (141 to 148 days of age) when subject R. D. was receiving pasteurized human milk, the mean change in weight was −2.1 gm. per day, although the mean change in weight during the previous 19 days (121 to 140 days of age) was +44.7

* This food was prepared by Lever Brothers Company.

gm. per day while somewhat larger amounts of the same food were being received. This subject gained only 5.0 gm. per day during a 5-day period (149-154 days of age) while receiving solids, including the soya bean food. With these exceptions, the rates of gain in weight varied between 14.2 and 44.7 gm. per day and the rate of gain during the majority of the periods of observation was greater than 20 gm. per day.

Nitrogen Balance Studies.—Intake of Nitrogen: With the exception of two periods of observation in which the desired intake of protein was not achieved (M. Ew., 183 to 195 days of age; L. M. 187 to 214 days of age), the daily intakes of protein of M. Ew. and L. M. varied between 1.31 and 1.42 gm. per kilogram. The daily intake of protein of M. R. varied between 1.54 and 1.88 gm. per kilogram, and that of R. D. between 2.01 and 2.33 gm. per kilogram.

Retention of Nitrogen: The two infants (R. D. and M. R.) with greater intakes of nitrogen generally had greater retentions of nitrogen. During four balance studies in which solid foods, but not the soya bean food, were given (M. Ew., balance studies beginning at 193 and 207 days of age; L. M., balance studies beginning at 197 and 211 days of age), the daily retentions of nitrogen were less than 50 mg. per kilogram, and in one of these (L. M., study beginning at 197 days of age) the nitrogen balance was negative. In all four of these studies the intakes of protein were low. In the remaining balance studies the relation of retention of nitrogen to intake of nitrogen was similar with each of the three feeding regimens (Figure).

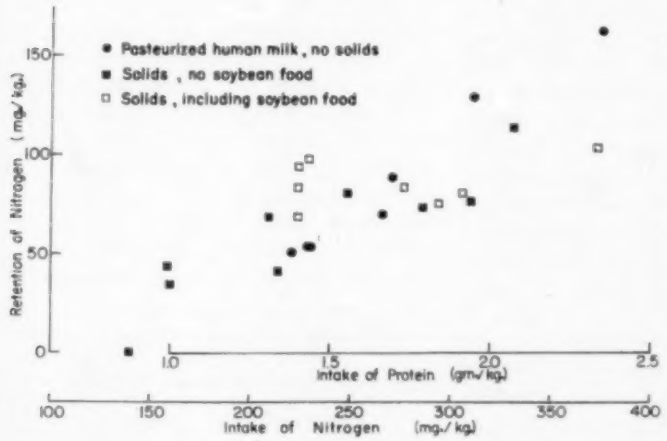
Comment

Although growth and retention of nitrogen by normal breast-fed infants during the first few months of life may generally be regarded as optimal, length of time during which human milk may be considered adequate as the sole food is not known.

Under the conditions of the present study, and despite the relatively low intakes of protein of two of the infants† (M. Ew. and L. M.), the rates of gain in weight and retention of nitrogen when 41% to 45% of the protein was derived from this soya bean food were quite similar to those observed when virtually all of the protein was derived from human milk.

More exact comparison of the equivalence of the protein of soya bean with that of human milk will necessitate the feeding of the same amount of protein derived from soya bean to one group of infants as is pro-

† We do not wish to imply that the intakes of protein of M. Ew. and L. M. (approximately 1.4 gm. per kilogram between 4½ and 8 months of age) are to be considered adequate for optimal growth and retention of nitrogen.



Daily retention of nitrogen in relation to intake of nitrogen. The intake of protein, calculated from the intake of nitrogen, is also shown.

vided in the form of human milk to another group. Such an approach appears to be warranted because the observations reported here have failed to demonstrate a great difference between the two foods as sources of protein for nourishment of small infants.

Summary and Conclusion

Four normal infants, 4 to 8½ months of age, were studied while receiving pasteurized human milk with or without additional solid foods of low protein content. In some of the studies an experimental soya bean food was substituted for other protein in sufficient amount to supply 41% to 45% of the total intake of nitrogen. An attempt was made to maintain constant the intake of calories, protein, carbohydrate, and fat throughout all the studies with a given infant.

The study failed to demonstrate superiority of feeding regimens that provided all, or nearly all, of the protein in the form of human milk over the regimen that provided 41% to 45% from the soya bean food.

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Treatment in a Child Guidance Clinic

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Introduction

In my experience, physicians in general practice and in specialties other than psychiatry are often poorly informed about and possess very little understanding of the activities and services of child guidance clinics. Surprisingly, this is also often true of psychiatrists trained only in adult psychiatry. This lack of understanding of the philosophy and rationale underlying such services all too often leads to unnecessary friction between clinics and private practitioners. While "educating" physicians regarding the services of child guidance clinics is not the complete answer to this problem, it does much to dissipate their misunderstandings and misconceptions.

This paper represents an attempt to discuss in a general way the commoner treatment procedures and patterns used in child guidance clinics. While there is considerable variation in specific details among clinics, it is possible to identify certain patterns and procedures which are generally accepted. The variations referred to are dependent upon such factors as availability of professional staff, orientation and training of staff members, local prejudices, and many other factors. Instead of discussing these variations an attempt will be made to confine the contents of this paper to the commoner patterns and procedures. Some of the problems related to treating patients in a child guidance clinic will also be discussed. Because it is difficult to fully understand current and emerging patterns of treatment without some knowledge of their developmental history, a brief historical background will also be included.

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Historical Development

Child guidance clinics, as known today, did not exist prior to the 20th century. Credit for the establishment of the first of these clinics belongs to Healy, who (in 1909) set up in Chicago The Juvenile Psychopathic Institute. This has since become the Institute for Juvenile Research. A few other cities shortly thereafter established similar facilities. Among these was the Louisville Child Guidance Clinic, which opened in 1913 and is still thriving. In 1917 Healy moved to Boston to open the Judge Baker Foundation, which has since become the Judge Baker Guidance Center.

Three years later (1920) impetus was given to this movement by the assistance and encouragement extended to interested communities by the Commonwealth Fund through the National Committee for Mental Hygiene. Under the auspices of this committee seven demonstration clinics were set up. The oldest of these (1921) The Cleveland Guidance Center, is still probably the best example of a *community* child guidance clinic. This committee was also responsible for the establishment of high standards for services and professional competence. All of these clinics were staffed by paid professional personnel consisting of a multiprofessional team composed of psychiatrists, psychologists, and psychiatric social workers.

During the last 35 years the number of clinics has steadily increased. After World War II assistance in the form of federal and state funds resulted in a rapid increase in the number and distribution of child guidance clinics. In spite of this rapid increase, however, as late as two years

ago 23 states were reported to have no clinics for children.

Problems

A. "Who is the Patient?"—Among the many complex problems with which clinics have been struggling for the past 50 years is that of deciding "Who is the patient?" when parents consult them about difficulties with one of their offspring. This question is complicated by several factors: 1. Disturbed children invariably have disturbed parents, and such parents are often more disturbed than their offspring. 2. Many of the parents consulting child guidance clinics are really seeking help for themselves and only bring the child as a "hostage" to save face in the eyes of their family, friends, and associates. 3. Parents often bring the *least* disturbed child in the family first to the clinic and only after months of therapy is this fact shared with the clinic staff.

In the process of attempting to answer this question child guidance clinics have, in my opinion, been going through a process of evolution. At first, most clinics (and private practitioners, too) regarded the child as *the patient* and devoted relatively little attention (by modern standards) to working with parents. Efforts to help the child varied from environmental manipulation to attempts to treat the child by classical psychoanalytical techniques, including use of the couch. While these efforts met with a measure of success, it became increasingly evident that the child patient had parents or parent surrogates who often complicated and sometimes frustrated efforts to help the child.

Out of these experiences came a shift in emphasis on the part of many clinics to regarding *parents* as *the patient*. According to this school of thought a child was but a plastic lump of clay to be molded for good or bad by his parents. Therefore, to help a child one needed only to "straighten out" his parents. Remnants of this viewpoint still persist. While there is a certain amount of truth in this idea (just enough to keep it alive), experience has gradually revealed that the emotional problems of children are usually too complex and too deeply internalized to be resolved solely by changes in their parents. Such a view also naively overlooks the role of the child in the etiology of his illness, and in this he may be a major contributor.

Recognition of the limitations of working with either child or parents alone resulted in attempts to work with both of them simultaneously. This is the most widely used procedure at the present time. Again, in using this approach, clinics have been plagued with the question, "Who is the patient?" A partial solution has been worked out whereby the child is regarded as the *primary* patient and his parents or parent surrogates as collateral patients. While there appears to be general agreement in defining what is meant by a primary patient, much confusion exists regarding the role and status of collateral patients. Primary patients are, of course, persons who are receiving therapy for their own problems. Collateral patients are persons who are theoretically receiving a *lesser* kind of therapy designed not to help them resolve their own emotional difficulties but to help them help the primary patient overcome his difficulties. Such a concept rather naively assumes that collateral patients are, in effect, assistant therapists and minimizes if not completely ignores their role in the primary patient's illness. Collateral therapy is supposedly primary patient-centered, and the worker is sternly admonished not to deal with the collateral patient's own problems. His role is to help the collateral patient better understand the primary patient and learn to handle relationships with him more effectively. Unfortunately, most of the parents who consult child guidance clinics are unable to do this until they have resolved many of their own emotional conflicts. The futility of giving advice to such parents has long since been amply demonstrated. In short, they need help for themselves before they can alter their feelings, attitudes, and behavior toward their offspring. Under such circumstances the harassed therapist

of the collateral patient is faced with the dilemma of either attempting to deal with his patient's problems directly or to refer the collateral patient elsewhere for such direct help while continuing to keep his own work with the parent child-centered. Many collateral patients are unwilling to accept such a transfer. Even when the transfer is made the attempt to seek help in one setting as a primary patient and in another as a collateral patient is often beyond the capacity of even the most versatile parent. In my experience, attempts to fill this dual role usually seriously impair the parents' ability to profit from either form of treatment.

Another contributing factor to this problem is the reluctance of many parents to accept the role of being a primary patient. They tend to see coming to the child guidance clinic very much as they see taking their child to his pediatrician. The clinic is being consulted about a disturbed and often disturbing child, not a disturbed parent. The same expectation of something being done to and for their child with a minimum of involvement on their part is present. While this attitude can be resolved during the process of evaluation, it is often a serious obstacle to the success of the clinic's efforts to help the family.

Because of these and other complications a new answer to the question "Who is the patient?" is gradually emerging. Many clinics are now becoming family-centered in their approach to treatment and would answer this question by stating the *family* is *the patient.* In terms of what we now know about the etiology and dynamics of emotional illness in children this answer would appear to be more rational than its predecessors and overcomes many of the limitations of former approaches to treatment with children. Each involved member of the family now becomes both a primary and a collateral patient. The therapist of each involved member of the family must be prepared to give help not only in assisting his patient to resolve his own difficulties but also to better understand the other members of his family and to handle relationships with them more satisfactorily.

Such family-centered therapy makes great demands upon the skill and resourcefulness of each therapist. It requires the availability of senior staff members to provide supervision and consultation to less trained members of the staff. The increasing frequency with which psychologists and psychiatric social workers are receiving training in the art of psychotherapy is contributing much to making such family-centered therapy feasible and effective.

B. Who Treats the Patient?—This brings us to the important question "Who treats the patient?" in a child guidance clinic. Traditionally children have been treated by child psychiatrists and to a less extent by psychologists, while parents were seen by psychiatric social workers. Today the trend is to disregard professional affiliations and to use staff members in terms of the skills they possess. Hence any member of the mental health team may be treating a child or his parents. This becomes increasingly true as the practice of family-centered therapy becomes more widespread in child guidance clinics. Since each involved member of the family is dealt with both as a primary patient and as a collateral patient, the question "Who treats the patient?" can only be answered by saying the *mental health team.*

In recent years clinics have been adding new members to this team. It now consists not only of psychiatrists, psychologists, and psychiatric social workers but also of social group workers, mental health nurses, and, in some places, remedial education therapists. These additions have enabled clinics to offer a more comprehensive pattern of services to the families seeking help from them.

Therapy Techniques

The therapeutic techniques employed in child guidance clinics vary in accordance with the training and orientation of their staff members. Staffs of some clinics are predominantly adherents to only one school of thought, whereas in others several schools

of therapy may be represented. Predominantly, however, child guidance clinics have been deeply influenced by the concepts of Meyer and Freud.

Therapeutic techniques have advanced from a beginning which was largely occupied with environmental manipulation as a means of influencing behavior to a more and more refined psychotherapy. In treating children a form of psychotherapy known as play therapy has been developed and is now generally used in treating children in the pre-school, latency, and early adolescent age groups. This involves the use of carefully selected play equipment to facilitate the establishment of rapport with the child and to encourage the overt expression of feelings, attitudes, and conflicts disturbing to him. These can be dealt with by the child's therapist in helping him resolve his difficulties.

Older adolescent children and parents are treated by the usual interview techniques. The intensity and depth of such therapy varies with needs of the patient and the skill of the therapist.

While most of the patients seen in child guidance clinics receive individual therapy, there is an increasing tendency to work with both children and adults in groups. This has come about not as a means of seeing more patients for a given period of time but because of a growing awareness that the needs of many patients are often better met by group therapy than individual therapy. Many patients receive both group therapy and individual therapy. Sometimes this is done concurrently and sometimes one follows the other. While the use of group therapy in resolving difficulties in peer relationships has now been amply demonstrated, its usefulness as a terminal experience to test out and solidify gains made in individaul therapy is now being extensively explored.

Although environmental manipulation continues to play an important role in therapy with children, it, alone, is seldom enough to resolve the child's difficulties. Nevertheless, because of complications in the life situation of a child and/or the nature and severity of his illness, it is sometimes the only feasible approach to at least partially relieving his distress. This can best be accomplished through the media of consultation services to parents, welfare workers, teachers, public health nurses, and other persons involved in working with the child.

In closing, a further word about therapy with parents and parent surrogates seems indicated. Such therapy is usually focused upon helping the parent better understand the nature of his or her relationship to the child and to develop more effective ways of handling these relationships. Inevitably the parent's therapist is forced to help him recognize and deal with many of his own conflicts and reactions. Not infrequently the outcome of therapy with the child hinges upon the success or failure of parents to resolve many of their own difficulties. Most children are unable to benefit from therapy until permitted to do so by their parents.

Summary

In this paper an attempt has been made to discuss treatment in a child guidance clinic from a developmental viewpoint. Some of the complex problems involved in such treatment have also been briefly discussed. Current trends and treatment procedures are briefly described.

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Some Viral Central Nervous System Diseases

Laboratory Studies with Emphasis on Aseptic Meningitis

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Introduction

Since the isolation and classification of Coxsackie viruses of Group B by Dalldorf [1] numerous investigations concerning the etiologic role of these agents as the cause of aseptic meningitis have been carried out both in the United States and abroad. In addition, during recent years evidence from different laboratories has also indicated that some specific types of ECHO viruses have been responsible for several outbreaks of aseptic meningitis.[2-10]

During the years 1956 and 1957, 245 patient with a central nervous system (CNS) disease of presumed viral etiology were seen at the James Whitcomb Riley Hospital for Children. These patients came from areas throughout Indiana, and we were unaware of an outbreak of epidemic proportions occurring in any region during the course of the two-year study.

The present study was undertaken in an attempt to recover viral agents from patients with a CNS involvement. Particular reference is made to a detailed laboratory investigation of 52 cases diagnosed as aseptic meningitis by the clinician. The report will, therefore, describe (*a*) the methods used for virus isolation, (*b*) the immune responses of patients to their own virus, and (*c*) attempts to demonstrate infection with the isolated strains in aseptic meningitis patients from whom viral agents could not be recovered.

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From the Department of Pediatrics, Indiana University Medical Center. Mr. A. C. Dwyer presently associated with Eli Lilly & Company.

Materials and Methods

Collections of Specimens.—Stools, spinal fluids, and blood samples were collected from 52 cases of aseptic meningitis. Attempts were made to obtain two stool specimens as early as possible after admission. Blood and spinal fluid samples were obtained upon admission and discharge of the patient. The stools and spinal fluids were frozen at —65 C and sera at —15 C until used.

Isolation and Identification of Viral Agents.—A 20% stool suspension was prepared in sterile distilled water. The crude suspension was dispensed in Pyrex tubes containing glass beads and then agitated on a mechanical shaker for 30 minutes. The suspension was clarified by centrifugation at 3,000 rpm. The supernatant fluid was decanted and centrifuged once more at 14,000 rpm for 30 minutes. Penicillin and streptomycin, 1,000 units per milliliter and 1,000μg. per milliliter, respectively, were added to the clear extract and then allowed to stand at room temperature for 30 minutes. One-half or 1 ml. of the supernatant fluid was inoculated into each of two culture tubes (human kidney or HeLa cells) and incubated at 36 C for several hours or overnight to allow virus adsorption onto the cells or permit the toxic substances normally present in the stool extract to exert their deleterious effect. If toxic effect was noted, several subcultures, at various intervals, were made to reduce toxicity yet permitting the virus, if present, to reveal itself. In the absence of toxic manifestation the fluid was replaced with fresh medium and the incubation continued until the cultures demonstrated a recognizable virus destruction. Four serial passages of the cell-fluid phase were carried out before the specimen was considered negative. The fluids from tissue culture cells showing virus damage were harvested and stored at —65 C until used. The unknown viruses in the form of 10^{-2} and 10^{-3} dilution were mixed with an equal amount of 1-in-10 dilution of individual type-specific chicken immune sera of poliomyelitis virus types prepared in this laboratory (titers >1:1,024 against 100 TCD_{50} of homologous virus). After the incubation of serum-virus mixtures for one hour at room temperature 0.2 ml. of the mixture was inoculated into each of two culture tubes and then incubated

at 36 C. Appropriate controls for cells, serum, and virus were also included. Final readings were made on the fifth day, even though virus controls showed complete degeneration at an earlier time. Whenever more than one type of poliomyelitis virus was suspected, combinations of the three types of poliomyelitis immune sera were used. Agents not neutralized by poliomyelitis virus antisera were tested, (1) for their ability to cause overt illness in infant mice, a characteristic of the Coxsackie viruses; (2) against Coxsackie antisera Types A_8, B_1 to B_5* and ECHO antisera types 1 to 14†; and identification was accomplished in the same manner as that described for poliomyelitis virus. In the former case 0.05 ml. each of infected tissue culture fluid and original specimen were inoculated intraperitoneally or subcutaneously into white infant mice less than 48 hours of age. The mice were observed daily for a period of two weeks or until signs of illness were noted. Deaths occurring in the first 24 hours were not considered as caused by a virus. Mice appearing ill were etherized, skinned, and eviscerated; those remaining healthy up to six days after inoculation of the test material were also killed at intervals thereafter. A 20% suspension of the whole carcass was then prepared and stored at —60 C until used. The procedures employed for recovery of virus in tissue culture from mouse tissues were essentially similar to those reported for the stool extracts. Agents recovered in this manner were considered as belonging to the Coxsackie viruses. Identification of Coxsackie viruses was then accomplished by the methods described above.

Human Kidney Cells (HK).—Fresh human kidney was obtained from patients on whom a ventriculoureteral shunt was performed for hydrocephalus. Within a short time after removal of the kidney the tissue was trypsinized according to the method of Youngner.[11] A 1-in-400 cell suspension (approximately 3.0×10^6 cells per milliliter) based on the packed cell volume was prepared in growth medium of the following composition: 2% calf serum, 94% lactalbumin hydrolysate in Earle's salt solution (0.5%), 4% $NaHCO_3$ (2.8%), and penicillin 100 units per milliliter with streptomycin 100μg. per milliliter. Tissue culture tubes and bottles were seeded with cells and kept stationary for seven to eight days in the incubator at 36 C until a contiguous sheet of cells was formed. Prior to the inoculation of culture tubes with the test material the growth medium in each tube was replaced with 1.5 ml. of maintenance medium composed of 96% mixture No. 199, 4% $NaHCO_3$ (2.8%), and antibiotics. Cultures could be maintained in this manner for as long as five weeks, provided the fluid was renewed periodically.

During the early phase of the study to be reported human kidney cells were predominantly used in attempts at isolation and identification of viral agents. The postsurgical kidney became unavailable when the neurosurgery department discontinued the ventriculoureteral shunt procedure. In a few instances cells derived from kidneys of children at postmortem examination (PHK), provided the death was not due to an infectious disease, were found equally suitable for virus isolation.

HeLa Cells.—HeLa stock cultures were grown on Eagle's basal medium[13] with 3% chicken serum, 7% calf serum, 5% egg ultrafiltrate,‡ 2% $NaHCO_3$ (2.8%), and the usual mixture of antibiotics. Under such conditions a fully developed outgrowth of cells was readily available for transfer after three to five days of incubation at 36 C. A continuous supply of HeLa cells was thus available by semiweekly transfer of the stock cultures. When needed, HeLa cell suspension prepared from stock cultures was transferred to tissue culture tubes and incubated in a stationary position at 36 C for not longer than four days, at which time a confluent sheet of cells was readily formed. The growth medium was then changed to maintenance composed of Eagle's basal medium supplemented with 2.5% calf serum. In contrast to human kidney cells, HeLa cells maintained in this manner failed to exhibit a healthy appearance after a period of one week. In most instances, therefore, parallel cultures of other tissue cells were also included for inoculation of the test material.

Monkey Kidney Cells (MK).—Rhesus monkey kidneys were aseptically removed and transported to the laboratory in mixture No. 199. Procedures employed for preparation of the cell cultures, the growth and maintenance media, and the growth conditions were essentially similar to those described for human kidney. MK cells were mainly used for virus titrations and neutralizing antibody determinations in the acute and convalescent sera of patients unless otherwise indicated.

Neutralization Test.—Antibody determinations in patients' sera were carried out in stationary MK cultures with their own virus recovered either in the stools or in the spinal fluids. Sera were heated at 56 C for 30 minutes before serial two-fold dilutions were prepared in mixture No. 199. To 0.3 ml. of serum dilution 0.3 ml. of virus suspension previously estimated to contain 100-150 TCD_{50} was

* Antisera for Coxsackie A_8, B_2, and B_4 were procured from Microbiological Associates, Inc. Chicken antisera for Coxsackie B_1, B_3, and B_5 were prepared in this laboratory.

† These were kindly supplied to us by Dr. H. A. Wenner and the National Foundation for Infantile Paralysis, Inc.

‡ Microbiological Associates, Inc., Washington, D. C.

added, and the mixture was kept at room temperature for one hour. Then 0.2 ml. of the mixture was added to each of the triplicate culture tubes, containing 1.5 ml. of MK maintenance medium and incubated at 36 C. Thereafter the tubes were checked daily for the appearance of cytopathogenic effect. The final readings were made not less than 72 hours after control virus cultures showed complete degeneration, and absence of cell destruction was taken as evidence of virus neutralization. Moreover, serial 10-fold virus titration and control culture tubes without virus were also included in each test. The 50% serum neutralizing end point titer was determined by the method of Reed and Muench.[18]

Results

Clinical Observations and the Frequency of Virus Isolations.—A total of 245 patients with CNS involvement was classified clinically into four groups: poliomyelitis, aseptic meningitis, encephalitis, and miscellaneous illnesses.

Of the 100 patients clinically diagnosed as poliomyelitis 86 were paralytic, and the remainder were classified as nonparalytic. Comparing the clinical impression with the final diagnosis, it was noted that the clinician was in error 11% of the time.

In spite of the fact that the clinical features of aseptic meningitis syndrome have been well described in the literature, an altered diagnosis in 17% of the cases seemed unavoidable. An attempt was made to separate the aseptic meningitis patient from the nonparalytic poliomyelitis patient on the basis of muscle spasm. The spasm seemed less severe and resolved more rapidly in the aseptic meningitis patient. Briefly, the aseptic meningitis patient had evidence of CNS irritation, was occasionally lethargic, rarely comatose, and in only one instance a convulsion was noted. Muscle weakness was thought to be present on occasion, but true paralysis was not evident. The weakness, if present, had disappeared at the time of discharge.

On occasion it was difficult to separate the 77 patients with a final diagnosis of encephalitis from those with aseptic meningitis. However, to the signs of meningeal irritation, the presence of stupor, delirium, encephalitic behavior, and/or convulsions were added to help support the diagnosis of encephalitis. Included in this group were two patients with probable diagnosis of postmeasles encephalitis, two with cerebellar encephalitis, and seven with mumps meningoencephalitis.

An attempt was also made to diagnose the 16 patients in the miscellaneous category. Four of these patients were thought to have Landry or Guillain-Berré syndrome; three had radiculomyelitis, and one had transverse myelitis.

Of 229 patients listed in Table 1, 113 (49.3%) yielded viral agents. Out of 86 paralytic patients, 78, and out of 14 nonparalytic patients, 11 yielded poliomyelitis virus in the stools (56 cases with Type I, and 1 with Type II in 1956; 26 with Type

TABLE 1.—*Number and Percentage of Patients with Central Nervous System Involvement and the Frequency of Viral Isolations from the Clinical Specimens During 1956 and 1957*

		Clinical Diagnosis			Specimens: Stools			Specimens: Spinal Fluids			
		Aseptic Meningitis	Encephalitis	Poliomyelitis	Aseptic Meningitis	Encephalitis	Poliomyelitis	Aseptic Meningitis	Encephalitis	Total Patients	Total Specimens
1956	No. positive	12	0	59	20	0	112 *	7	0	71	139
	No. studied	25	52	65	40	67	126	36	74	142	343
1957	No. positive	9	1	32	8	2 †	55	5	0	42	70
	No. studied	27	23	35	25	33	59	41	29	87	187
Totals per cent positive		40.4	1.4	91.0	43.0	2.0	90.3	15.6	0	49.3	39.4

* 107 poliomyelitis virus, plus 5 untypable cytopathogenic agents.
† 2 cytopathogenic agents were untypable.

I, and 6 with Type III in 1957); 16 yielded Coxsackie viruses; 5 yielded ECHO virus types; and 3 excreted cytopathogenic agents which have as yet not been identified.

As listed in Table 1, from 77 encephalitis patients only 1 patient yielded an untypable cytopathogenic agent in the duplicate stool samples. The complement-fixation tests performed on the paired sera of 41 of these patients failed to reveal the presence of complement-fixing antibodies in the lowest serum dilution (1 in 4) when western equine encephalitis, eastern equine encephalitis, St. Louis encephalitis, and lymphocytic choriomeningitis (21 out of 41 patients) antigens were employed.

Finally, not listed in the Table are the 16 patients with miscellaneous illnesses, 4 of whom yielded cytopathogenic agents which were untypable in this laboratory.

Effectiveness of Methods Employed in Viral Isolation from the Spinal Fluids and Stools.—Two methods of virus isolation from the spinal fluids of patients with aseptic meningitis were used. In the first method at least one spinal fluid from each patient was inoculated concurrently into HK cultures and HeLa cells. Daily microscopic examinations of the culture tubes were made until cellular degeneration was apparent. Four successive blind passages of cell-fluid phase were carried out before it was concluded that virus was absent. In general, the cytopathogenic effect of some viruses on primary isolation in cultures of HK or PHK epithelium developed very slowly throughout the monolayer, i. e., 7 to 35 days later. In certain instances, however, complete destruction of the cell sheet was observed in a shorter time during the second or third HK passages. In contrast, HeLa cultures were either affected by the cytopathogenic agents within two to five days after inoculation or were completely refractory.

In the second method attempts were made to infect suckling mice with the spinal fluids. Two or three mice from each litter were killed on the sixth and eighth day after inoculation to obtain tissues for passage.

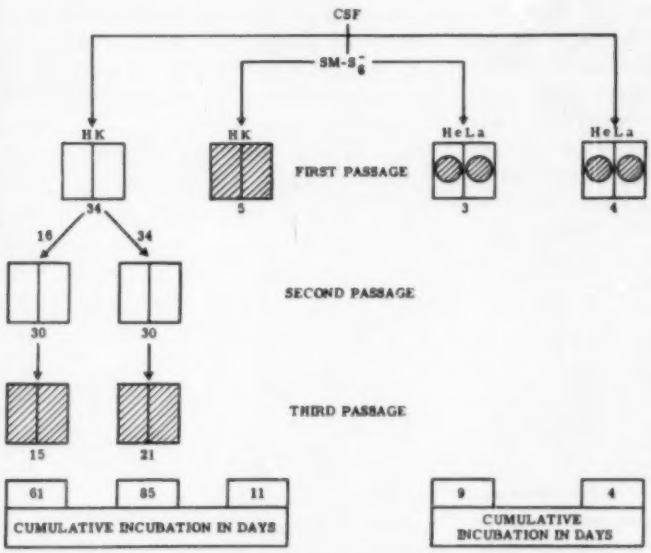
TABLE 2.—*Results of Virus Isolation from Twenty-One Aseptic Meningitis Patients and the Neutralizing Antibody Response to Their Own Virus*

		Virus Isolation				Neutralizing Titers of Serum *	
Patient	Age, Yr.	Stools	Spinal Fluid	Sera Collected	Days from Onset	Acute	Convalescent
1	3½	NA	A_2	11	24	<4	<8
2	6	B_2	B_2	8	277	<4	16
3	12	B_2	B_2	1	19	40	<1,024
4	6	—	B_2	1	15	20	512
5	8	B_4	B_4	7	14	80	512
6	3	B_4	B_4	4	10	25	256
7	8	B_4	—	7		40	-
8	10	B_4	—	15	41	10	160
9	3½	B_3	—	8	16	>32	316
10	5	B_3	B_3	4	9	32	80
11	3	B_3	B_3	3	8	40	160
12	7	B_3	B_3	0	7	>32	512
13	4	B_3	—	1	5	15	100
14	6	B_4	—	5	29	20	32
15	1	B_3	B_3	2		<8	
16	4½	B_3	—	7	42	15	20
		ECHO					
17	11	7	—	1	9	4	4
18	8	9	NA	8	17	40	80
19	5	9	NA	4		<8	
20	10	9	9	1	28	<50	316
21	½	NA	9	7		4	

* Titers expressed as reciprocal of initial serum dilution.
NA = not available.
— = negative.

The remainder of the mice were kept under observation for two weeks. In most instances, however, there was no evidence of illness in inoculated mice during the observation period in spite of the fact that seven Coxsackie virus strains were isolated by subsequent passages of mouse suspension into HK or HeLa cultures. By this method, in most instances, the cytopathogenic effect of mouse-passage virus in cell cultures was noted in a much shorter interval as compared with those seen in cultures inoculated directly with the spinal fluid. However, exceptions to such findings were not infrequent. In fact, three of the Coxsackie strains appeared quite early in tissue culture when spinal fluids from each of three patients, (10, 5, and 11, Table 2), were inoculated into HK or HeLa cultures. Consquently, no pronounced difference in the final results could be provided by using either method for the isolation of Coxsackie viruses in these studies. However, both methods of isolation were employed in case either one would prove unsatisfactory for recovery of virus.

Because of the possibility of accidental or latent infection of mice, information concerning these points was specifically sought during these studies. First, mice inoculated with the test material were kept in a separate room. Furthermore, control mouse suspension was prepared and inoculated into HK and HeLa cultures at the same time as in the test mice. Under such conditions all control specimens yielded negative results. Second, in all instances the virus recovered through both methods from a single spinal fluid was shown to be the same.



Diagrammatic representation of the Coxsackie B$_5$ virus isolation from the spinal fluid of a patient (No. 12) with aseptic meningitis.

* Coxsackie B$_5$ virus was isolated from the stools of this patient.

SM-S$_6^-$ = Suckling mice (<48 hrs. old) inoculated subcutaneously with 0.03 cc. of cerebral spinal fluid, sacrificed on 6th day with no overt illness.

34 = Indicating two roller-tube cultures of human kidney cells were inoculated and incubated for 34 days at 37° C. without viral CPE. Numbers appearing on either side of each arrow indicate the day on which blind passage of cell-fluid phase was made.

15 = Positive viral CPE after 15 days.

5 = Positive viral CPE in HeLa cells after 3 days.

The results obtained from one experiment using the methods adopted above are diagrammatically shown in the Figure. As can be seen, Coxsackie B_5 virus arising as a result of mouse inoculation with the spinal fluid of a patient (No. 12) showed complete cytopathogenic effects in HK cultures after an incubation of five days, whereas the same virus reisolated from the original spinal fluid in cultures of HK epithelium failed to produce cellular degeneration until the third passage level. Thereafter the interval before the cytopathogenic effect was observed after inoculation of virus decreased to three to four days during the fourth or fifth HK passages. In contrast, when the virus established from the suckling mouse passage and the original spinal fluid were each inoculated into HeLa cultures virus damage was observed in three and four days, respectively. It should be noted that viruses obtained from each CSF tested did not necessarily behave in the same manner as described in this experiment. Accordingly, 12 viral agents from the spinal fluids of 21 patients (Table 2) were successfully isolated using the methods described, and in the case of Patient 20 by inoculation of MK cultures. Of these, 10 were identified as members of the Coxsackie family and 2 as ECHO 9 virus by means of neutralization tests with the appropriate antisera in tissue culture.

The cytopathogenic agents obtained from the stools of 18 patients presented in Table 2 were obtained in a manner similar to the first method described above. Viral agents were recovered from stools in HK cultures in five instances; HeLa cultures, in seven instances, and MK cells in six instances. No virus could be isolated from the stools of Patient 4, using the tissue culture methods described, although the spinal fluid of this patient yielded Coxsackie B_2. It is noteworthy that all of the Coxsackie strains and one ECHO 9 (Patient 20) isolated from the stools by tissue culture technique were shown to be pathogenic for infant mice.

Neutralizing Antibodies.—Paired sera were obtained from 17 patients who yielded cytopathogenic agents in their stools, spinal fluids, or both. The initial sera in most instances were drawn when the patients were admitted to the hospital, although the time interval between the onset of illness and admission varied with each patient. The results shown in Table 2 present data on the antibody response of the patients to their own virus recovered during the acute illness. It is seen that a significant rise in serum neutralizing antibodies was readily demonstrable in paired sera of 10 patients (47.6%). Conversely, there was little or no difference in the neutralizing antibody titer of the paired sera from Patients 1, 2, 10, 14, 16, 17, and 18. An additional three follow-up sera from each of three patients (5, 12, and 17) obtained eight months after onset were tested for neutralizing antibodies. Patient 5 had antibodies without a subsequent change in titer, whereas in Patient 12 a moderate drop in neutralizing antibodies occurred, but the titer of Patient 17 remained unchanged.

Neutralizing Antibody Levels in 23 Patients (Under 11 Years of Age) from Whom Viral Agents Could Not Be Isolated.—In view of our repeated failure to isolate viral agents from 31 aseptic meningitis cases, attempts were made to demonstrate the development, in 23 of 31 patients, of specific neutralizing antobodies for the strains isolated from patients with aseptic meningitis.

Virus strains employed in the neutralization tests consisted of Coxsackie B_2, B_4, B_5; ECHO 7 and 9. In addition, prototype strains of poliomyelitis virus Types I, II, and III were also included. Fourfold dilutions of each acute and convalescent serum were tested against approximately 100 TCD_{50} of each immunologic type that came from aliquots of one virus pool.

Although 10 of 23 patients possessed poliomyelitis virus neutralizing antibodies only in high titer in both sera, in none of the remainder was there a rise in Types I,

TABLE 3.—*Neutralizing Antibody Levels in Paired Sera of Twenty-Three Children with Aseptic Meningitis from Whom Viral Agents Were Not Obtained* *

Category of Patients †	Number of Patients with Neutralizing Antibodies Against Indicated Viruses over Number of Patients in Category				
	Coxsackie			ECHO	
	B_2	B_4	B_5	7	9
A	5/13 ‡	7/13 §	3/13	3/13	1/13
B	12/22	8/22	15/22	5/22	11/22

* Paired sera were available from 23 of 31 patients.

† Category A: Patients with antibody titers of 1:64 or greater in both sera. Category B: Patients with acute serum titer of 1:4 or less and convalescent serum of 1:8 or less.

‡ One of these patients showed fourfold or greater rise in titer against B_4 virus.

§ One patient demonstrated eightfold rise in titer against B_4 virus.

II, and III antibodies between the acute and convalescent phase sera. Since these sera were not tested for the presence of complement-fixing antibodies to the three types of poliomyelitis virus, no serologic evidence of poliomyelitis virus infection could be offered.

The magnitude of neutralizing antibody levels to the strains of Coxsackie and ECHO viruses in the paired sera of 23 patients (Table 3) justified the classification of this group into two categories. Category "A" consisted of 13 of 23 patients who possessed high antibody titers (1 in 64 or greater) against the strains of Coxsackie and ECHO viruses in both sera. In this connection paired sera of one patient in addition to possessing antibodies at such levels to Coxsackie B_2, B_5, and ECHO 7, also revealed a slightly greater than fourfold rise in titer to Coxsackie B_4 virus. Another patient showed a rising antibody level of eightfold against Coxsackie B_5 virus. On the other hand, category "B," comprising those patients with acute serum titer of 1 in 4 or less and convalescent serum of 1 in 8 or less, constituted the largest segment (22 of 23 patients) in this study, indicating the lack of a possible association of the selected strains with the majority of cases.

Comment

The results reported in this study reaffirm the findings of other workers [14-21] in regard to the implication of Coxsackie viruses of Group B being among the variety of agents capable of producing benign aseptic meningitis.

Although the number of patients with aseptic meningitis during the two-year period was small, it was possible to recover a variety of cytopathogenic agents from 21 (40.4%) of 52 patients. Of the 21 agents isolated 16 belonged to the Coxsackie viruses, while the remainder were classified as ECHO virus types.

The isolation of Coxsackie A_9 virus from the spinal fluid of one patient, though not substantiated by the serologic evidence, may suggest the possibility that the etiology of the illness for which the patient was hospitalized was due to the isolated agent. This experience is in line with that of Davis and Melnick,[22] who isolated A_9 virus in two instances from the spinal fluid and stools of patients with aseptic meningitis in Connecticut. Two of the three patients shedding B_2 virus had appreciable rise in homotypic antibody titer; three of the four patients excreting B_4 virus showed a 10-fold titer rise in the convalescent sera against the isolated type, and the development of antibody during the convalescence in four of eight patients yielding B_5 virus provided evidence supporting the etiologic role of B_5 virus in the syndrome of aseptic meningitis. In general, a correlation between the presence of virus in the clinical specimens and a rise in antibodies was observed in 10 (47.6%) out of 21 patients. It is noteworthy that all B_5 virus strains were encountered during the summer of 1956. Others [19-20] have likewise presented evidence associating B_5 virus with outbreaks of aseptic meningitis occurring in the midwestern part of the United States.

With one exception there was no serologic evidence that the illness in patients shedding ECHO virus types was attributable to infection with the isolated viruses. At present

the exact role of some of the ECHO types as infecting agents is difficult to define since they have been commonly encountered in healthy children.[23] On the other hand, observations made by several investigators[4-9] seem to justify the association of ECHO 9 virus with a clinical illness manifested by a rubella-like rash with or without aseptic meningitis. In our studies rash was observed in one of the cases from whom ECHO 9 was isolated.

Since the majority of aseptic meningitis patients in the present study did not excrete viral agents, the possibility of infection with other microbial agents was not entirely excluded. However, it was speculated that some might have acquired infection with the strains which had been isolated from patients experiencing the same illness. While only 2 of 23 patients responded with an increase in neutralizing antibodies in paired sera, the remainder possessed either a high level of antibodies to one or more strains or revealed negligible titers in both sera. Obviously, on the basis of the neutralization test alone, it is difficult to assess the relative importance of the findings from each of two patients who did not shed virus but who revealed antibody rises against the strains of Coxsackie B_4 and B_5, respectively. In the light of these findings the possibility that these two patients might have experienced either a dual infection or a single infection caused by an antigenically related strain should not be overlooked. On the other hand, a high level of multiple antibodies in sera of children may indicate the occurrence of repeated infection with different types of enteric viruses which are so prevalent in nature.

Summary

During the investigation, which extended over a two-year period, clinical specimens were collected from 245 patients with CNS involvement. A total of 117 (47.7%) cytopathogenic agents was recovered in tissue culture. From 100 patients with poliomyelitis, poliomyelitis virus was isolated from 78 of the paralytic and 11 of the nonparalytic cases. Among the poliomyelitis virus types isolated in 1956, 56 were Type I, and 1 was Type II; while in 1957, 26 were Type I, and 6 were Type III.

Detailed study was carried out with respect to the viral etiology of 52 aseptic meningitis cases. Successful isolations of Coxsackie and/or ECHO virus types were made in 21 (40.4%) of these patients. The Coxsackie virus types consisted of one Type A_9, three type B_2, four type B_4, and eight type B_5. The ECHO virus types included one Type 7, and four Type 9. No other strains of Coxsackie or ECHO groups could be isolated, nor was there a poliomyelitis virus present in the specimens from any of these patients. The demonstration in 10 cases of specific rise in neutralizing antibodies for the virus isolated, plus failure to establish any other etiological diagnosis strongly suggested that the CNS signs of these patients were due to the isolated agents.

High titers of neutralizing antibodies against one or more strains isolated from aseptic meningitis patients were found to be present in the paired sera of 13 of 23 patients, who were not shedding viral agents. A serologic evidence of Coxsackie virus infection could be demonstrated in two patients only; one developed a fourfold rise in titer against Coxsackie B_4 virus, while the other showed an eightfold rise to Coxsackie B_5 virus.

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Leg Volume Changes Observed in Hyaline Membrane Disease

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The pathophysiology of the neonatal respiratory distress syndrome has been largely inferred from postmortem appearances in infants showing pulmonary hyaline membranes at autopsy. Little is known of earlier changes occurring soon after birth, and essentially nothing of any prenatal or perinatal disturbances of physiology. But, since roentgenological and other studies have defined the clinical entity relatively clearly, investigation of earlier phases and in infants who survive is increasingly possible.

The association of nenonatal respiratory distress with an appearance of edema has been noted for some time.[1] Although the nature of the hyaline material composing the membranes found at autopsy has yet to be completely defined, fibrin is present.[2] This finding lends support to the idea that the hyaline membranes come at least in part from inside the body rather than from aspiration of foreign material. If the protein or fibrin-containing material in the alveoli is a local transudation, a similar movement of fluid from the vascular system might be demonstrable in other parts of the body also. This paper describes an attempt at such a demonstration by a simple method giving objective measurements.

Fig. 1.—Apparatus for determination of volume of a segment of leg.

Material and Methods

The apparatus used permitted measurement of the water displaced by immersion of the extremity to a constant level (Fig. 1). An indelible mark was put around the baby's leg 2 or 3 cm. below the knee (Cado Flomaster pen). The beaker was filled with tepid water and the meniscus adjusted to a determined level by suction. The baby's leg was immersed to the mark and the water displaced was sucked into the weighed bottle. The volume of displaced water was determined by reweighing the bottle.

In any determination the leg was immersed 10 to 15 times. The adequacy and precision of the immersions were judged and graded as 1+ to 4+, and immersions

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Sample Data on One Determination of Leg Volume

Precision of Immersion	Weight of Water and Bottle, Gm.	Weight of Bottle, Gm.	Weight of Water, Gm.
4+	128.4	80.9	47.5
4+	127.5	80.9	46.6
2+		81.1	
3+		81.1	
4+	125.6	81.4	44.2
4+	126.2	81.7	44.5
4+	130.0	81.9	48.1
4+	127.4	82.1	45.3
1+		82.1	
4+	127.6	81.7	45.9
4+	126.8	83.1	43.7
		Total	365.8
		Mean	45.7
		S. D.	1.6
		S. E.	.6

graded less than 3+ were excluded. The volume of the segment of the extremity was the arithmetical mean of the weights of the displaced water of 5-10 satisfactory immersions. A sample determination is shown in the Table. The standard error of the measurement calculated for a number of determinations was 1 gm. of water.

Experiments demonstrated that the temperature of the water within the limits used in the determinations could not explain the observed differences. The position of the normal infant before the determination, whether on one side or the other, head up or head down, did not significantly affect the results. Nor, by determinations on both legs, did handling of the extremity during immersion account for the results. It was impossible to determine whether or not holding the infant with the feet in a very dependent position during the three to five minutes necessary for the determination accounted for the results, for a control determination with the infant in any other position could not be made with the described apparatus.

Results

Sequential determinations of the volume of a constant segment of an extremity were compared in nine normal-term and premature infants and in six term and premature infants with the *neonatal respiratory distress syndrome* or hyaline membrane disease. The abnormal infants were selected on the basis of a history of maternal complications, progressive respiratory distress starting soon after birth and associated with retractions and cyanosis, and a chest roentgenogram showing the characteristic reticulogranular pattern. One infant in the present group died and had hyaline material lining the alveolar ducts.

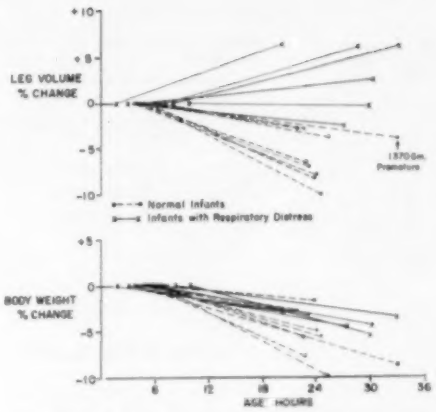

Fig. 2.—Leg volume and body weight changes in six infants with the neonatal respiratory distress syndrome and nine normal-term and premature infants during the first 24 hours of life. The mean time of the initial observation was 5⅓ hours (range 1¾ to 9¾ hours); the mean time of the second observation was 26 hours (range 20¼ to 33 hours).

Figure 2 indicates the per cent changes observed in leg volume and body weight in the nine normal infants and the six infants with respiratory distress in the first 24-34 hours after birth. During this period when none of the sick infants were being fed, but a few of the normal infants received water, formula, or breast feeding, all of the infants lost weight. The segment of the leg of the normal infants decreased in size in an amount paralleling their loss of body weight. On the other hand, the sick infants had a relative increase in the volume of the extremity at the same time as their total body weight was decreasing. This measured increase in the size of the extremity was usually accompanied by development of an edematous appearance, which could not otherwise be objectively quantitated, nor,

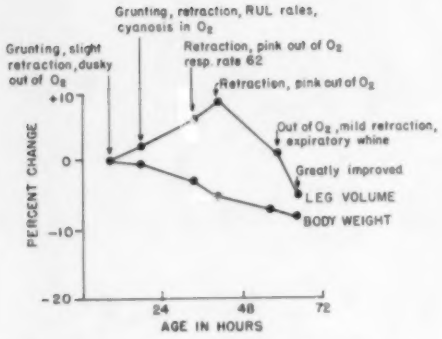

Fig. 3.—The course of leg volume and body weight of an infant with the neonatal respiratory distress syndrome. A 4 lb. 8 oz. (2,040 gm.) boy, born by vertex of a 25-year-old white gravida VII, para VII at 37 weeks' gestation. Resuscitation was by inversion. Cry and first breath were immediate; however, grunting respiration with retraction was apparent within the first hour. The respiratory rate increased; retractions became severer, and cyanosis more intense. A chest roentgenogram at 8 hours revealed the picture associated with hyaline membrane disease. There was no appreciable roentgenographic change at 18 hours, but by 2½ days the chest films were essentially normal.

in some cases, even be demonstrated by pitting.

Further, in a few infants with the *neonatal respiratory distress syndrome* who were studied more frequently, the increases in the volume of the leg paralleled the course of the disease (Fig. 3).

Comment

A suggestive relationship between changes in leg volume and pulmonary changes was demonstrated in these six infants. Inasmuch as the relative increase in leg volume was associated with a normal weight loss, the developing edema cannot be ascribed to acquisition and retention of total body fluid after birth, but rather to redistribution of the fluid present at birth. This redistribution might take place with or without changes in the size of the intravascular compartment. The fact that the increasing leg volume was associated in some of the infants with the development of clinical edema makes the possibility that there is a shift of fluid from vascular to extravascular compartments more likely. Whether this represents a decrease in size of a normal vascular compartment or a decrease toward normal of an initially large vascular compartment is not answered by the present study.

Also, since the factors necessary for development of the *neonatal respiratory distress syndrome* appear to be present at the time of birth, results of study of the sick infant after birth may reflect basic pathophysiology or may only reflect changes resulting from or subsequent to a more basic process. Indeed, it is possible that the peripheral edema is a result of the disturbed pulmonary physiology rather than coexistent with it. However, since the infant at risk is not amenable to study before birth, it is only by such observations that theories relating to cause may eventually lead to effective prevention in the unborn child. This simple method and the results of its use with a few infants are published in the hope of stimulating such observations by others rather than as establishing the mechanism by which hyaline membranes are produced in newborn infants.

Summary

A method for determining and following the volume of a leg segment of newborn infants is described.

The leg volume and body weight of nine normal term and premature infants decreased approximately equally during the first 24 to 34 hours after birth.

A relative increase in the size of the leg during a time of decreasing weight was found in six infants with the *neonatal respiratory distress syndrome* usually associated with pulmonary hyaline membrane disease.

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Linear Body Proportions

A Roentgenographic Study

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. . . . "the child" as revealed by mass statistics of any sort is a bit of fiction. Reality is found only in the growth changes of individual children: Mary, John, Greta, Hans, Giovanna, Antonio, Rose and Isidore.—C. B. DAVENPORT (*Sc. Month.* 52: 197-202 [March] 1941)

The concept of differences in linear bodily proportions is a familiar one. We refer to persons as "long-legged" or "short-trunked" in the same definitive sense that we say "tall" or "short." We are also well aware that changes in proportions occur during growth, since the body form of the young child differs from that of the adult in more than size. As a continuation of the investigation of growth of the subjects being studied at the Child Research Council, this present study will deal with linear segmental proportions, their changes during growth, and the variations observed in the young adult.

Previous publications [1,2] on the growth in length of the major long bones of the extremities refer to the study of proportions or "relative lengths" as a necessary part of a description of body build. This was well demonstrated in Dr. Edith Boyd's publication [3] describing the changes in the bodily proportions of one boy as he grew through childhood to adult life. It is difficult, however, for even the trained observer to judge the length of segments of the body in terms of "per cent of height." If comparisons between individuals are to be made meaningful, these relative lengths must be made measurable. This has been done by use of the equation

$$\frac{\text{Measured bone length}}{\text{height}} \times 100 = \text{relative bone length.}$$

Thus differences in the height of individuals of the same age are negated and it becomes possible to describe a child as "relatively long-legged" at any age regardless of his total height.

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Material

The measurements of the long bones of the extremities during the growth period, uninterrupted since 1935, have been taken from several thousand sets of roentgenograms. Technique was described before [1] and has not been altered. The method of measuring bone lengths was also described before, and these measurements have been made and checked by me. Measurements of height and sitting height, as well as total length and crown-rump length of the infants, were taken from the anthropometric data, and the relative lengths were computed. These data were then considered as equivalents of the relative lengths of the upper and lower arm (humerus and radius lengths), upper and lower leg (femur and tibia lengths), and the trunk (crown-rump length or sitting height) in discussing bodily proportions.

Standards

The limitations of data such as these are obvious. In spite of there being large numbers of measurements for each age for both boys and girls, these are from seriatim roentgenograms of about 200 persons, some of whom are still infants and less than half of whom have completed their long-bone growth. Therefore, while this is a longitudinal study in design, the number of years of follow-up on any one person varies from less than 1 year to as many as 17 to 20 years. This same situation obtained in the selection of "standards"

TABLE 1.—*Boys: Smoothed Percentiles and Observed Range for Relative Length of the Long Bones of the Extremities (%)*

A. Arm

$$\frac{\text{Bone Length Between Epiphyseal Plates (cm.)}}{\text{Height (cm.)}} \times 100$$

Age		Humerus							Radius						
Yr.	Mo.	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %
0	2	11.82	12.32	12.80	13.11	13.44	10.85	14.18	9.95	10.20	10.45	10.70	10.90	9.47	11.17
0	4	12.02	12.51	13.02	13.30	13.65	11.78	14.21	9.95	10.20	10.47	10.72	10.96	9.68	11.17
0	6	12.30	12.82	13.25	13.56	13.90	11.66	14.22	9.95	10.22	10.50	10.82	11.06	9.85	11.54
1	0	13.39	13.79	14.07	14.38	14.71	12.62	15.00	10.40	10.68	10.95	11.25	11.50	10.34	12.06
1	6	14.11	14.41	14.64	14.94	15.26	13.58	15.60	10.74	11.00	11.20	11.48	11.78	10.42	12.14
2	0	14.57	14.85	15.05	15.35	15.65	14.14	16.09	10.96	11.20	11.40	11.68	12.00	10.77	12.47
2	6	14.84	15.14	15.34	15.65	15.96	14.39	16.37	11.14	11.38	11.58	11.87	12.19	10.89	12.54
3	0	15.09	15.37	15.59	15.91	16.21	14.58	16.47	11.30	11.55	11.74	12.05	12.35	11.07	12.63
3	6	15.29	15.58	15.83	16.14	16.41	14.64	16.53	11.46	11.70	11.88	12.19	12.49	11.30	12.73
4	0	15.47	15.76	16.04	16.33	16.59	15.09	16.75	11.60	11.83	12.01	12.31	12.62	11.26	12.88
4	6	15.63	15.92	16.22	16.49	16.74	15.21	17.34	11.69	11.93	12.13	12.43	12.73	11.46	12.99
5	0	15.77	16.07	16.38	16.64	16.88	15.23	17.45	11.78	12.03	12.23	12.54	12.83	11.51	13.11
5	6	15.89	16.19	16.52	16.77	17.00	15.50	17.60	11.86	12.11	12.32	12.63	12.92	11.33	13.13
6	0	15.99	16.30	16.63	16.88	17.12	15.09	17.39	11.93	12.19	12.40	12.72	13.01	11.79	13.31
6	6	16.07	16.40	16.74	16.99	17.22	15.58	17.66	12.00	12.26	12.47	12.78	13.09	11.59	13.40
7	0	16.15	16.50	16.85	17.09	17.32	15.82	17.81	12.06	12.33	12.55	12.84	13.16	11.70	13.43
7	6	16.23	16.59	16.95	17.19	17.42	15.72	17.91	12.12	12.40	12.62	12.91	13.24	11.69	13.57
8	0	16.30	16.68	17.05	17.28	17.52	15.81	18.29	12.18	12.46	12.69	12.97	13.31	11.81	13.53
8	6	16.37	16.77	17.15	17.37	17.61	15.79	18.03	12.24	12.52	12.76	13.03	13.37	11.87	13.49
9	0	16.43	16.85	17.24	17.46	17.70	15.95	18.03	12.30	12.58	12.83	13.09	13.43	11.84	13.70
9	6	16.49	16.93	17.33	17.55	17.79	15.81	18.31	12.35	12.64	12.90	13.16	13.48	11.87	13.87
10	0	16.55	17.01	17.41	17.63	17.87	16.06	18.25	12.40	12.69	12.96	13.22	13.53	12.13	13.88
10	6	16.61	17.08	17.49	17.70	17.94	16.13	18.59	12.44	12.74	13.03	13.28	13.58	12.05	13.88
11	0	16.67	17.15	17.57	17.77	18.01	16.27	18.63	12.48	12.79	13.10	13.34	13.62	12.06	14.00
11	6	16.71	17.22	17.65	17.84	18.07	16.33	18.77	12.52	12.83	13.16	13.40	13.67	12.23	13.96
12	0	16.75	17.29	17.73	17.90	18.14	16.28	18.54	12.56	12.87	13.21	13.46	13.72	12.20	14.09

$$\frac{\text{Bone Length Including Epiphyses (cm.)}}{\text{Height (cm.)}} \times 100$$

10	0	17.82	18.23	18.62	18.96	19.31	17.26	19.59	13.40	13.59	13.87	14.17	14.46	13.01	14.52
10	6	17.89	18.30	18.68	19.02	19.37	17.35	19.59	13.44	13.64	13.91	14.24	14.55	13.04	14.92
11	0	17.96	18.38	18.75	19.09	19.44	17.46	19.87	13.49	13.70	13.97	14.32	14.64	13.09	15.05
11	6	18.03	18.46	18.83	19.16	19.52	17.49	19.76	13.55	13.76	14.03	14.41	14.74	13.15	15.16
12	0	18.11	18.55	18.91	19.25	19.61	17.29	20.02	13.62	13.83	14.10	14.50	14.85	13.29	15.20
12	6	18.19	18.65	19.00	19.34	19.71	17.83	20.18	13.69	13.91	14.18	14.60	14.97	13.54	15.27

13	0	18.27	18.75	19.09	19.44	19.82	18.01	20.19	13.77	13.99	14.27	14.71	15.11	13.58	15.48
13	6	18.36	18.85	19.19	19.54	19.93	17.83	20.15	13.86	14.08	14.36	14.82	15.25	13.70	15.49
14	0	18.45	18.96	19.30	19.65	20.05	18.05	20.36	13.96	14.18	14.47	14.95	15.37	13.83	15.69
14	6	18.55	19.07	19.41	19.77	20.16	18.04	20.46	14.05	14.28	14.56	15.05	15.45	13.92	15.89
15	0	18.65	19.18	19.52	19.88	20.25	18.27	20.38	14.14	14.37	14.64	15.14	15.49	13.68	15.90
15	6	18.75	19.29	19.63	19.96	20.32	18.51	20.62	14.21	14.45	14.72	15.21	15.52	14.18	15.88
16	0	18.83	19.35	19.73	20.03	20.37	18.48	20.67	14.27	14.52	14.78	15.24	15.53	13.66	15.85
16	6	18.88	19.38	19.80	20.09	20.38	18.09	20.47	14.31	14.54	14.82	15.23	15.52	14.30	15.87
17	0	18.90	19.38	19.84	20.11	20.37	18.14	20.66	14.33	14.54	14.82	15.21	15.49	14.26	15.97
17	6	18.89	19.36	19.83	20.10	20.34	18.18	20.48	14.32	14.51	14.79	15.16	15.43	14.25	15.67
18	0	18.85	19.32	19.80	20.06	20.25	18.27	20.48	14.28	14.46	14.70	15.08	15.35	14.14	15.67

B. Leg

$$\frac{\text{Bone Length Between Epiphyseal Plates (cm.)}}{\text{Height (cm.)}} \times 100$$

Age		Femur							Tibia						
Yr.	Mo.	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %
0	2	13.75	14.31	15.16	15.70	16.00	13.18	16.08	11.14	11.82	12.26	12.70	13.20	10.70	13.76
0	4	15.00	15.54	15.95	16.45	16.78	14.15	17.29	11.95	12.48	12.90	13.25	13.70	11.41	13.98
0	6	15.75	16.25	16.71	17.15	17.55	15.64	18.81	12.64	13.12	13.50	13.78	14.13	12.33	14.64
1	0	17.36	17.75	18.13	18.48	18.85	17.05	19.58	13.90	14.27	14.68	14.95	15.30	13.60	15.56
1	6	18.34	18.68	19.06	19.46	19.85	17.57	20.38	14.84	15.19	15.59	15.82	16.10	14.18	16.61
2	0	19.18	19.51	19.84	20.22	20.62	18.52	21.22	15.67	16.01	16.28	16.48	16.80	15.26	17.12
2	6	19.77	20.13	20.48	20.85	21.27	19.08	22.42	16.28	16.57	16.82	17.02	17.31	15.67	17.53
3	0	20.27	20.63	21.02	21.36	21.84	19.57	22.43	16.69	16.97	17.22	17.46	17.72	16.00	17.92
3	6	20.70	21.08	21.50	21.84	22.34	20.32	23.08	17.03	17.31	17.56	17.84	18.12	16.62	18.46
4	0	21.12	21.50	21.93	22.27	22.77	20.79	23.57	17.35	17.63	17.89	18.20	18.46	16.92	19.21
4	6	21.52	21.91	22.33	22.68	23.17	21.14	23.71	17.62	17.90	18.19	18.51	18.78	17.23	19.21
5	0	21.89	22.30	22.70	23.04	23.52	21.35	24.30	17.86	18.15	18.47	18.78	19.08	17.40	19.81
5	6	22.23	22.63	23.03	23.38	23.86	21.85	24.57	18.07	18.38	18.71	19.03	19.35	17.19	19.74
6	0	22.55	22.95	23.34	23.69	24.18	22.05	24.98	18.27	18.60	18.93	19.27	19.61	17.98	20.13
6	6	22.86	23.27	23.63	24.00	24.46	22.14	25.04	18.45	18.80	19.13	19.51	19.86	17.72	20.76
7	0	23.14	23.54	23.91	24.30	24.72	22.53	25.53	18.62	18.99	19.33	19.73	20.10	17.79	20.79
7	6	23.38	23.80	24.17	24.57	24.96	22.66	25.46	18.78	19.17	19.53	19.94	20.33	18.15	21.22
8	0	23.60	24.03	24.41	24.80	25.18	22.85	26.32	18.94	19.34	19.72	20.15	20.54	18.23	21.36
8	6	23.78	24.22	24.62	25.00	25.39	23.32	25.71	19.10	19.51	19.90	20.33	20.74	18.45	21.01
9	0	23.96	24.38	24.79	25.19	25.60	23.46	26.36	19.24	19.66	20.08	20.51	20.93	18.59	21.76
9	6	24.12	24.53	24.95	25.37	25.79	23.72	26.20	19.38	19.81	20.24	20.68	21.11	18.57	21.93
10	0	24.26	24.68	25.09	25.52	25.96	23.74	26.96	19.51	19.95	20.40	20.84	21.28	19.34	22.07
10	6	24.40	24.82	25.23	25.67	26.12	24.31	26.57	19.64	20.09	20.55	21.00	21.45	18.97	22.25
11	0	24.53	24.95	25.37	25.81	26.27	24.22	27.66	19.76	20.22	20.70	21.16	21.61	19.02	22.44
11	6	24.65	25.07	25.51	25.95	26.41	24.05	27.14	19.88	20.34	20.84	21.30	21.76	19.27	22.65
12	0	24.77	25.18	25.64	26.09	26.55	24.07	27.38	20.00	20.46	20.98	21.44	21.90	19.39	22.68

TABLE 1.—*Boys: Smoothed Percentiles and Observed Range for Relative Length of the Long Bones of the Extremities (%)*—Continued

B. Leg

$$\frac{\text{Bone Length Including Epiphyses Plates (cm.)}}{\text{Height (cm.)}} \times 100$$

Age		Femur							Tibia						
Yr.	Mo.	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %
10	0	26.90	27.34	27.72	28.18	28.77	26.15	29.36	22.22	22.55	22.93	23.37	23.77	21.84	25.12
10	6	27.03	27.49	27.90	28.34	28.92	26.20	29.65	22.38	22.72	23.14	23.60	24.04	21.98	25.26
11	0	27.16	27.65	28.08	28.51	29.07	26.55	29.90	22.54	22.91	23.35	23.83	24.31	22.12	25.33
11	6	27.30	27.80	28.26	28.68	29.23	26.52	30.12	22.70	23.11	23.56	24.05	24.57	22.42	25.65
12	0	27.44	27.93	28.44	28.85	29.38	26.36	29.91	22.87	23.31	23.77	24.26	24.81	22.62	25.77
12	6	27.57	28.05	28.61	29.02	29.52	27.12	30.43	23.03	23.51	23.97	24.46	25.03	22.82	25.83
13	0	27.68	28.15	28.74	29.16	29.64	27.23	30.59	23.18	23.70	24.16	24.64	25.22	22.75	25.93
13	6	27.76	28.23	28.84	29.26	29.74	27.47	30.57	23.29	23.83	24.30	24.76	25.35	23.04	26.05
14	0	27.82	28.29	28.90	29.33	29.81	27.54	30.50	23.36	23.91	24.38	24.84	25.44	22.74	26.14
14	6	27.84	28.32	28.93	29.37	29.86	27.58	30.47	23.38	23.94	24.39	24.87	25.48	22.99	26.28
15	0	27.85	28.32	28.94	29.38	29.88	27.54	30.97	23.37	23.93	24.38	24.88	25.51	22.51	26.50
15	6	27.84	28.31	28.92	29.35	29.87	27.55	30.45	23.35	23.92	24.37	24.89	25.53	23.31	26.47
16	0	27.81	28.28	28.87	29.31	29.84	27.62	30.11	23.32	23.90	24.35	24.88	25.54	22.44	26.27
16	6	27.75	28.24	28.79	29.25	29.79	27.58	30.26	23.28	23.83	24.28	24.86	25.54	23.27	26.37
17	0	27.66	28.18	28.71	29.18	29.73	27.35	30.17	23.22	23.74	24.19	24.82	25.53	22.96	26.09
17	6	27.54	28.08	28.63	29.09	29.65	27.04	29.62	23.14	23.60	24.06	24.75	25.51	22.98	26.09
18	0	27.38	27.98	28.56	29.00	29.55	27.02	29.88	23.03	23.45	23.91	24.66	25.48	22.66	25.96

for length of these bones,[2] and again it was necessary to treat each of these figures as unitary values in arriving at standards for relative lengths. These are presented as percentile values in Table 1 (boys) and Table 2 (girls). Dr. Boyd's standards for relative sitting height for boys and girls are given in Tables 3 and 4.

It was of more than casual interest to us to compare the present standards for relative lengths of the long bones with the mean values as published[1] in 1943. At that time the data were few, differences in standards for boys and girls had not been demonstrated, and the narrow range of values for bone length divided by height at each age was the subject of emphasis. These unsmoothed mean values for each half-year from 6 months to 12 years, presumed to be quite tentative because of the small number of persons in each age interval, are shown for the femur and radius in Figure 1 as solid lines, along with the present median values for boys and girls (broken and dotted lines) as given in Tables 1 and 2. The additional data which were added in the years subsequent to 1943 have validated the statement that the forearm bones are relatively longer in boys than in girls and have demonstrated that the median values for boys and girls are nearly alike for the relative bone lengths of the other segments before adolescence. It is indeed gratifying to find there are such areas of investigation where the so-called "normal" range and the measure of central tendency need not be considered totally inadequate because the data are limited.

General Considerations

Having set up zones of variation against which the relative lengths of an individual can be assessed, certain general observations are pertinent.

1. Although the total range of variation in relative lengths is small (about 3% of height) for any given age, it is not a "fanning" zone of distribution with increasing age as are most linear measurements. The differences in the relative lengths of the trunk and the segments of the extremities are as demonstrable in the newborn infant as they are in the adult or the older child at any age.

2. While it is obvious that height (or length), sitting height (or crown-rump length), and the lengths of all the major long bones of the extremities are increasing in size as the child grows, the rates of growth are not alike. Thus the long bones of both the upper and the lower extremities become an increasingly greater per cent of height from infancy to late adolescence, while the relative trunk length becomes an increasingly shorter per cent of height during that same period.

3. The increase in the relative lengths of the bones of the extremities and the decrease in relative crown-rump length and sitting height are the most rapid between 6 months of age and about 3 years. The positioning of children for x-ray examinations during this period is usually difficult, and anthropometric measurements are also less reliable than in the older cooperative child. Thus it is surprising that the values for relative lengths are reasonably consistent, since small fluctuations in the measured lengths will produce major differences in the values for the relative lengths.

That these relative lengths are usually reasonably consistent is illustrated in Figure 2, where the length and height of three girls as well as their relative segmental lengths—crown-rump, humerus, radius, femur, and tibia—are graphed against the percentile zones set up from the standards. It will be noted that the birth lengths of these girls were about the same (49.7, 49.7, and 49.0 cm.), that they were of the same length at 6 months of age (65.2, 65.3, and 65.2 cm.), and that it was only after 9 months of age that their heights became appreciably different. At one year of age the heights were 74.2, 73.8, and 72.9 cm. While there are fluctuations in the individual curves for the first year of life, it is evident that the long-trunked child in 2*A*

TABLE 2.—*Girls: Smoothed Percentiles and Observed Range for Relative Length of the Long Bones of the Extremities (%)*

A. Arm

$$\frac{\text{Bone Length Between Epiphyseal Plates (cm.)}}{\text{Height (cm.)}} \times 100$$

Age		Humerus							Radius						
Yr.	Mo.	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %
0	2	12.23	12.56	12.85	13.23	13.68	11.38	13.97	9.86	10.12	10.41	10.62	10.96	9.53	11.56
0	4	12.32	12.67	13.14	13.48	13.89	11.96	14.45	9.85	10.12	10.40	10.63	10.98	9.55	11.58
0	6	12.62	13.05	13.46	13.73	14.10	12.22	14.44	9.97	10.17	10.39	10.65	11.01	9.73	11.56
1	0	13.37	13.70	14.10	14.40	14.75	12.33	15.45	10.25	10.53	10.79	10.99	11.27	10.00	12.08
1	6	14.00	14.25	14.64	14.95	15.25	13.48	15.80	10.46	10.78	11.02	11.24	11.49	10.12	12.02
2	0	14.45	14.70	15.06	15.30	15.55	14.22	16.14	10.65	10.98	11.19	11.44	11.69	10.25	12.30
2	6	14.73	15.05	15.35	15.57	15.77	13.97	16.83	10.82	11.16	11.33	11.61	11.86	10.12	12.50
3	0	14.94	15.30	15.59	15.79	15.98	14.67	16.17	10.96	11.31	11.47	11.75	12.00	10.73	12.47
3	6	15.13	15.49	15.79	16.00	16.19	14.92	16.53	11.10	11.44	11.61	11.88	12.13	10.93	12.50
4	0	15.29	15.64	15.97	16.19	16.40	15.01	16.58	11.22	11.55	11.74	12.00	12.24	10.88	12.63
4	6	15.43	15.78	16.12	16.36	16.61	15.20	16.95	11.33	11.65	11.86	12.11	12.35	11.17	12.65
5	0	15.56	15.90	16.25	16.53	16.80	15.28	17.11	11.43	11.74	11.98	12.22	12.45	11.27	13.07
5	6	15.67	16.01	16.38	16.67	16.97	15.16	17.23	11.51	11.83	12.08	12.31	12.54	11.35	12.79
6	0	15.78	16.13	16.51	16.80	17.11	15.41	17.38	11.59	11.91	12.17	12.38	12.62	11.35	12.81
6	6	15.88	16.25	16.63	16.92	17.23	15.51	17.93	11.67	12.00	12.26	12.46	12.68	11.47	13.33
7	0	15.98	16.36	16.74	17.04	17.34	15.68	18.23	11.76	12.08	12.34	12.53	12.75	11.64	13.46
7	6	16.09	16.47	16.85	17.14	17.44	15.63	17.62	11.83	12.16	12.42	12.60	12.81	11.59	14.34
8	0	16.20	16.58	16.96	17.25	17.55	15.48	18.20	11.89	12.23	12.49	12.67	12.88	11.52	13.50
8	6	16.30	16.70	17.06	17.36	17.66	15.63	18.05	11.96	12.30	12.56	12.75	12.94	11.55	12.98
9	0	16.41	16.83	17.17	17.49	17.76	15.52	18.03	12.03	12.37	12.64	12.83	13.02	11.72	13.35
9	6	16.51	16.94	17.27	17.62	17.88	15.73	18.48	12.11	12.44	12.72	12.91	13.11	11.83	13.74
10	0	16.62	17.03	17.37	17.71	17.99	15.41	18.42	12.20	12.51	12.81	13.00	13.20	11.96	13.42
10	6	16.74	17.12	17.46	17.77	18.07	15.96	18.49	12.29	12.60	12.90	13.09	13.29	11.90	14.02
11	0	16.86	17.20	17.53	17.81	18.11	15.88	18.59	12.38	12.69	12.99	13.18	13.38	12.06	13.65
11	6	16.97	17.28	17.60	17.84	18.12	16.28	18.43	12.48	12.78	13.08	13.27	13.47	12.34	13.68
12	0	17.07	17.35	17.63	17.87	18.12	15.91	18.43	12.58	12.87	13.17	13.36	13.56	12.18	13.66

$$\frac{\text{Bone Length Including Epiphyses (cm.)}}{\text{Height (cm.)}} \times 100$$

10	0	17.73	18.20	18.51	18.78	19.11	16.67	19.70	13.12	13.33	13.71	13.95	14.18	12.83	14.36
10	6	17.85	18.32	18.63	18.91	19.25	16.96	20.15	13.22	13.45	13.83	14.06	14.29	12.94	15.07
11	0	17.97	18.45	18.75	19.05	19.37	16.96	19.65	13.32	13.57	13.94	14.15	14.39	12.97	14.56
11	6	18.08	18.56	18.87	19.18	19.49	17.80	19.78	13.41	13.67	14.04	14.24	14.48	13.10	14.67
12	0	18.18	18.66	18.98	19.29	19.60	17.14	20.47	13.49	13.76	14.12	14.32	14.57	13.21	15.25
12	6	18.28	18.75	19.08	19.38	19.68	17.74	20.45	13.56	13.85	14.19	14.33	14.64	13.35	15.28

13	0	18.36	18.82	19.17	19.46	19.76	17.31	20.50	13.61	13.92	14.24	14.44	14.70	13.21	15.18
13	6	18.36	18.86	19.25	19.52	19.83	17.75	20.43	13.64	13.96	14.27	14.47	14.74	13.28	15.11
14	0	18.34	18.86	19.30	19.57	19.87	17.96	20.53	13.66	13.98	14.28	14.49	14.77	13.39	15.24
14	6	18.29	18.85	19.30	19.57	19.88	17.87	19.80	13.67	13.98	14.28	14.51	14.78	13.28	15.08
15	0	18.25	18.85	19.29	19.56	19.88	17.16	20.57	13.67	13.98	14.27	14.52	14.78	13.19	15.21
15	6	18.24	18.84	19.27	19.55	19.88	17.20	20.55	13.66	13.97	14.26	14.52	14.78	13.82	14.81
16	0	18.24	18.83	19.25	19.52	19.87	17.25	20.56	13.65	13.95	14.25	14.52	14.77	13.61	15.07
16	6	18.23	18.81	19.22	19.49	19.86	17.50	20.56	13.63	13.93	14.23	14.51	14.76	13.60	15.04
17	0	18.23	18.79	19.18	19.46	19.83	17.92	20.56	13.60	13.91	14.21	14.50	14.75	13.56	15.01

B. Leg

$$\frac{\text{Bone Length Between Epiphyseal Plates (cm.)}}{\text{Height (cm.)}} \times 100$$

Age		Femur							Tibia						
Yr.	Mo.	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %
0	2	14.96	15.36	15.72	16.18	16.60	14.59	17.26	11.65	12.18	12.64	13.16	13.61	10.73	13.88
0	4	15.72	16.08	16.44	16.82	17.25	15.22	17.90	12.27	12.76	13.20	13.65	14.06	11.15	14.33
0	6	16.38	16.72	17.04	17.38	17.82	16.03	18.49	12.79	13.24	13.66	14.06	14.45	12.33	14.91
1	0	17.61	17.96	18.30	18.71	19.12	17.44	19.46	14.08	14.43	14.76	15.10	15.43	13.52	15.25
1	6	18.50	18.87	19.18	19.62	20.02	18.22	20.45	14.94	15.26	15.56	15.89	16.22	14.34	16.73
2	0	19.26	19.64	19.95	20.38	20.75	19.24	21.21	15.60	15.90	16.22	16.54	16.88	15.14	17.25
2	6	19.90	20.25	20.60	20.95	21.30	19.54	21.81	16.09	16.40	16.71	17.08	17.42	15.84	17.86
3	0	20.38	20.76	21.14	21.45	21.81	19.60	22.19	16.49	16.82	17.12	17.53	17.87	15.42	18.27
3	6	20.82	21.20	21.58	21.90	22.27	20.21	22.67	16.85	17.17	17.49	17.93	18.26	15.87	18.72
4	0	21.22	21.61	21.98	22.30	22.70	20.77	23.06	17.16	17.50	17.82	18.28	18.62	16.22	19.14
4	6	21.60	21.99	22.36	22.69	23.09	21.18	23.45	17.44	17.80	18.13	18.59	18.93	16.68	19.19
5	0	21.98	22.36	22.72	23.07	23.46	21.60	23.65	17.70	18.09	18.44	18.89	19.23	16.88	19.82
5	6	22.32	22.69	23.04	23.42	23.81	21.66	24.21	17.94	18.36	18.73	19.17	19.50	17.01	19.69
6	0	22.63	23.02	23.36	23.73	24.15	22.18	24.73	18.17	18.62	19.01	19.42	19.75	17.71	19.65
6	6	22.92	23.33	23.65	24.03	24.43	21.84	24.81	18.40	18.85	19.24	19.65	19.98	17.33	20.75
7	0	23.19	23.61	23.94	24.31	24.71	22.20	25.06	18.63	19.07	19.46	19.86	20.20	17.68	20.89
7	6	23.46	23.88	24.23	24.58	24.97	22.11	25.42	18.86	19.29	19.66	20.07	20.40	17.74	21.08
8	0	23.69	24.11	24.48	24.85	25.22	22.57	25.55	19.07	19.50	19.85	20.28	20.61	18.10	21.18
8	6	23.91	24.33	24.72	25.08	25.44	22.80	26.25	19.27	19.69	20.05	20.49	20.82	18.29	21.01
9	0	24.09	24.51	24.92	25.28	25.65	23.00	26.04	19.46	19.87	20.25	20.69	21.03	18.49	21.34
9	6	24.25	24.67	25.08	25.45	25.83	22.85	26.74	19.66	20.06	20.45	20.90	21.24	18.47	21.69
10	0	24.40	24.81	25.24	25.62	26.00	23.32	26.30	19.85	20.25	20.66	21.11	21.45	18.85	21.77
10	6	24.54	24.95	25.40	25.79	26.16	23.42	26.61	20.04	20.43	20.86	21.32	21.66	18.98	22.15
11	0	24.66	25.08	25.55	25.95	26.30	23.65	26.80	20.23	20.61	21.05	21.51	21.87	19.23	22.34
11	6	24.77	25.20	25.70	26.11	26.44	23.69	26.57	20.42	20.79	21.23	21.70	22.06	19.30	22.19
12	0	24.88	25.33	25.85	26.27	26.58	24.08	27.10	20.61	20.97	21.41	21.88	22.25	19.31	22.38

TABLE 2.—*Girls: Smoothed Percentiles and Observed Range for Relative Length of the Long Bones of the Extremities (%)*—Continued

B. Legs

$$\frac{\text{Bone Length Including Epiphyses (cm.)}}{\text{Height (cm.)}} \times 100$$

Age		Femur							Tibia						
Yr.	Mo.	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %	10% %	25% %	50% %	75% %	90% %	Min. %	Max. %
10	0	26.84	27.26	27.77	28.12	28.50	25.78	28.74	22.34	22.78	23.30	23.82	24.27	21.69	24.74
10	6	26.98	27.41	27.93	28.29	28.69	25.82	29.32	22.50	22.95	23.47	23.98	24.45	21.78	24.84
11	0	27.09	27.53	28.07	28.43	28.85	26.07	29.29	22.63	23.09	23.61	24.09	24.60	22.01	25.08
11	6	27.18	27.64	28.16	28.55	28.99	26.13	29.21	22.72	23.19	23.71	24.17	24.71	22.06	25.03
12	0	27.26	27.73	28.23	28.64	29.10	26.74	29.51	22.78	23.26	23.79	24.23	24.79	22.26	25.22
12	6	27.32	27.79	28.28	28.71	29.17	26.43	29.46	22.80	23.28	23.82	24.26	24.82	22.19	25.11
13	0	27.36	27.83	28.32	28.76	29.20	26.54	29.61	22.80	23.30	23.81	24.28	24.82	22.00	25.35
13	6	27.38	27.86	28.33	28.78	29.22	26.43	29.53	22.79	23.30	23.79	24.26	24.80	21.97	25.20
14	0	27.39	27.87	28.33	28.78	29.23	26.03	29.62	22.76	23.29	23.76	24.21	24.77	21.60	25.42
14	6	27.38	27.87	28.31	28.76	29.24	26.44	29.56	22.73	23.27	23.71	24.14	24.72	21.81	25.14
15	0	27.37	27.86	28.28	28.72	29.24	26.53	29.76	22.69	23.24	23.66	24.06	24.66	21.55	25.23
15	6	27.35	27.84	28.24	28.66	29.21	27.46	29.19	22.65	23.20	23.64	23.99	24.59	22.07	24.76
16	0	27.32	27.80	28.19	28.60	29.17	26.23	29.38	22.61	23.16	23.62	23.91	24.53	21.43	25.13
16	6	27.29	27.75	28.13	28.53	29.11	26.23	29.38	22.57	23.12	23.60	23.86	24.46	21.43	24.84
17	0	27.26	27.70	28.07	28.46	29.05	26.23	29.39	22.52	23.08	23.58	23.81	24.40	21.43	24.84

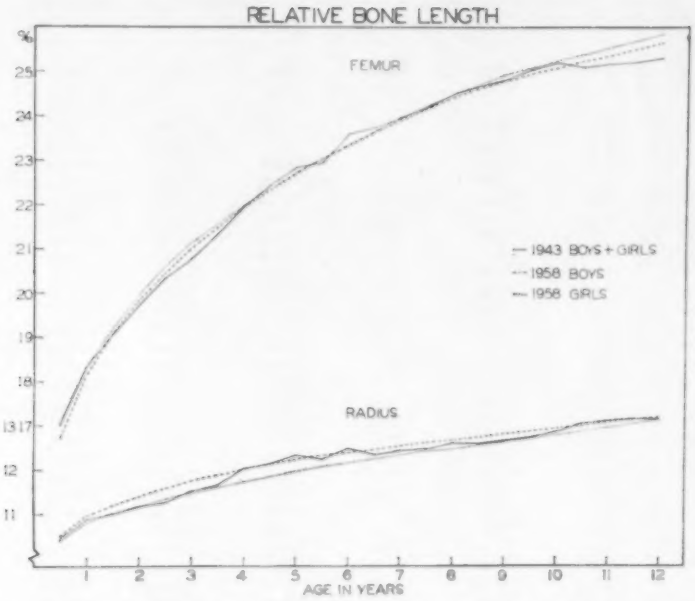


Fig. 1.—The mean values for relative lengths of the femur and radius (calculated from the equation: $\frac{\text{measured bone length (cm.)}}{\text{height (cm.)}} \times 100 = \text{relative bone length}$) are graphed against age. The solid lines represent the values from the data of the boys and girls in the Child Research Council study series in 1943. The broken lines (boys) and dotted lines (girls) represent the mean values from the data at this time.

is readily distinguished from the short-trunked girl. The relative lengths of the segments of the arms and legs for these two girls are the opposite of their relative trunk length—long arms and legs in the short-trunked girl and short arms and legs in the long-trunked girl. The third girl is of more nearly average proportions for the trunk and legs in spite of her slower rate of growth in total height as seen in 2*A*.

4. It should be borne in mind that since height is the divisor in the computation of all the relative lengths, there will be a reciprocal relationship between relative trunk length and relative leg length. If the value for relative trunk length is far below the median for a given age, the values for the femur and tibia will almost certainly be well above the median for that age. If the measurement of crown-rump

TABLE 3A.—*Boys: Smoothed Percentiles for Relative Crown-Rump Length (%)*

Age		10%	25%	50%	75%	90%	Min.	Max.
Yr.	Mo.	%	%	%	%	%	%	%
0	1	63.50	64.70	66.30	67.50	68.50	61.5	70.3
0	6	64.20	65.40	66.40	67.50	68.30	60.6	69.6
0	9	63.00	64.30	65.40	66.40	67.40	62.0	69.8
1	0	61.90	63.00	64.00	65.00	66.00	60.3	66.7
1	6	60.20	61.30	62.10	63.00	64.00	59.5	65.4
2	0	58.50	59.80	60.60	61.80	62.80	56.0	63.8
2	6	57.00	58.30	59.30	60.60	61.80	56.0	62.1
3	0	55.80	57.10	58.20	59.60	60.50	55.4	61.1

TABLE 3B.—*Boys: Smoothed Percentiles for Relative Sitting Height (%)*

Age		10%	25%	50%	75%	90%	Min.	Max.
Yr.	Mo.	%	%	%	%	%	%	%
1	6	59.85	60.40	61.40	62.40	63.00	59.6	64.4
2	0	58.55	59.30	60.34	61.15	61.60	58.2	61.7
2	6	57.25	58.25	59.24	60.05	60.70	56.5	61.4
3	0	56.30	57.25	58.19	59.05	59.85	55.5	60.9
3	6	55.50	56.35	57.24	58.15	59.00	55.2	61.0
4	0	54.75	55.68	56.39	57.35	58.36	53.5	58.6
4	6	54.15	55.23	55.94	56.84	57.86	52.6	58.2
5	0	53.72	54.79	55.55	56.44	57.36	51.4	58.0
5	6	53.29	54.35	55.17	56.04	56.96	52.4	57.8
6	0	52.86	53.91	54.80	55.64	56.30	51.4	57.4
6	6	52.43	53.47	54.44	55.24	55.96	50.7	57.6
7	0	52.00	53.03	54.09	54.86	55.54	50.5	56.3
7	6	51.73	52.67	53.75	54.30	55.16	49.4	55.6
8	0	51.50	52.39	53.41	54.16	54.81	50.8	55.8
8	6	51.27	52.16	53.09	53.84	54.49	50.3	55.4
9	0	51.04	51.95	52.79	53.54	54.20	49.3	54.5
9	6	50.81	51.75	52.51	53.26	53.94	49.7	54.8
10	0	50.58	51.54	52.25	53.00	53.70	49.8	54.6
10	6	50.35	51.32	52.00	52.75	53.46	49.2	54.4
11	0	50.00	51.09	51.76	52.51	53.22	49.3	54.1
11	6	49.55	50.85	51.53	52.28	52.98	48.7	54.7
12	0	49.35	50.60	51.31	52.06	52.74	48.6	53.9
12	6	49.30	50.35	51.10	51.85	52.50	48.2	53.4
13	0	49.25	50.15	50.90	51.65	52.35	48.1	53.6
13	6	49.20	50.05	50.85	51.65	52.35	47.8	53.6
14	0	49.15	50.00	50.85	51.65	52.35	47.1	53.8
14	6	49.15	49.95	50.90	51.65	52.35	47.3	53.7
15	0	49.20	50.05	51.05	51.65	52.45	47.9	54.3
15	6	49.30	50.24	51.20	51.80	52.57	48.5	53.2
16	0	49.42	50.43	51.36	51.95	52.71	47.8	54.6
16	6	49.57	50.62	51.52	52.09	52.85	48.4	54.8
17	0	49.76	50.81	51.68	52.22	52.90	49.0	55.0
17	6	50.00	51.00	51.84	52.34	53.13	48.6	53.8
18	0	50.19	51.15	52.00	52.45	53.27	48.8	54.8
19	0	50.32	51.33	52.16	52.66	53.55	49.2	54.1
20	0	50.35	51.37	52.20	52.85	53.83	49.5	55.0

length or sitting height did not include some of the soft tissues of the buttocks and part of the upper femurs, the sum of the femur, tibia, and crown-rump or sitting height measurements should be nearly equal to the height measurement and the sum of these relative lengths should be about 100%. Actually in these studies the reciprocal relationship between relative leg length and relative trunk length is evident at all ages but is less than an exact negative correlation. For example, the coefficients of correlation between the relative sitting height and the relative femur length for

TABLE 4A.—*Girls: Smoothed Percentiles for Relative Crown-Rump Length (%)*

Age		10%	25%	50%	75%	90%	Min.	Max.
Yr.	Mo.	%	%	%	%	%	%	%
0	1	64.25	65.55	66.80	68.50	70.10	59.9	71.9
0	6	63.60	65.40	66.40	67.85	69.00	60.0	72.8
0	9	62.20	63.80	64.90	65.80	66.70	60.3	71.0
1	0	61.30	62.90	64.15	65.00	66.00	59.9	69.0
1	6	59.35	61.10	62.30	63.30	64.20	58.8	67.0
2	0	57.80	59.30	60.45	61.70	62.50	56.6	63.8
2	6	56.30	57.70	58.80	60.30	61.10	55.0	62.9
3	0	54.90	56.30	57.40	59.20	60.30	53.1	62.0
3	6	53.80	55.10	56.70	58.50	59.00	51.8	60.3

TABLE 4B.—*Girls: Smoothed Percentiles for Relative Sitting Height (%)*

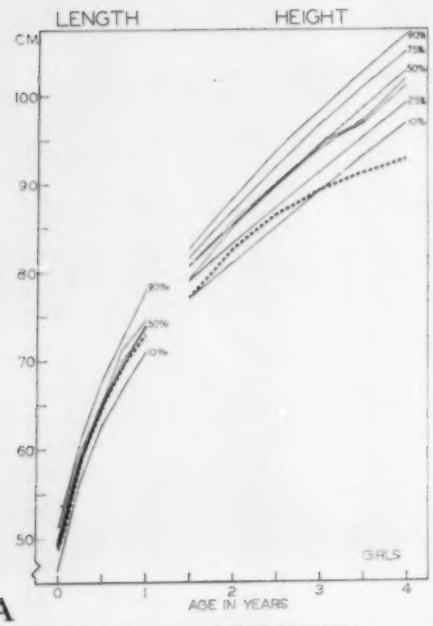
Age		10%	25%	50%	75%	90%	Min.	Max.
Yr.	Mo.	%	%	%	%	%	%	%
1	6	59.25	60.40	61.60	62.40	63.30	57.4	64.4
2	0	58.50	59.30	60.20	60.85	61.70	57.3	63.2
2	6	57.50	58.35	59.00	59.70	60.65	57.3	61.6
3	0	56.50	57.50	58.20	58.80	59.70	55.4	60.3
3	6	55.50	56.65	57.40	58.20	58.80	54.8	59.2
4	0	54.90	55.80	56.60	57.65	58.25	53.0	59.3
4	6	54.45	55.30	56.10	57.10	57.80	53.9	58.6
5	0	54.00	54.85	55.70	56.60	57.35	52.1	58.5
5	6	53.60	54.40	55.30	56.15	56.90	52.0	58.9
6	0	53.25	53.95	54.90	55.75	56.45	51.4	58.6
6	6	52.90	53.55	54.55	55.35	56.05	51.4	57.8
7	0	52.55	53.20	54.10	54.95	55.70	51.0	57.0
7	6	52.20	52.90	53.70	54.55	55.35	50.5	56.9
8	0	51.85	52.60	53.35	54.20	55.05	50.0	56.6
8	6	51.50	52.30	53.00	53.90	54.80	50.4	57.1
9	0	51.20	52.00	52.70	53.65	54.45	48.7	56.2
9	6	51.00	51.75	52.45	53.40	54.00	49.5	55.9
10	0	50.80	51.50	52.20	53.15	53.60	48.7	55.7
10	6	50.60	51.25	52.00	52.90	53.20	49.0	54.9
11	0	50.40	51.05	51.80	52.65	53.15	48.6	55.1
11	6	50.20	50.90	51.60	52.50	53.00	49.4	54.6
12	0	50.00	50.75	51.65	52.45	52.95	48.0	53.3
12	6	50.00	50.80	51.75	52.50	53.00	49.0	54.6
13	0	50.05	50.90	51.85	52.55	53.10	49.2	55.5
13	6	50.15	51.05	51.95	52.70	53.20	48.5	54.4
14	0	50.25	51.20	52.05	52.85	53.50	49.5	54.8
14	6	50.45	51.40	52.20	53.00	53.65	48.7	55.1
15	0	50.65	51.60	52.45	53.15	53.75	49.6	55.3
15	6	50.80	51.70	52.55	53.30	53.85	49.9	54.8
16	0	50.90	51.80	52.60	53.40	53.90	50.1	55.1
17	0	50.90	51.90	52.70	53.50	54.00	49.7	55.9
18	0	50.90	51.90	52.76	53.55	54.06	50.5	55.7
19	0	50.90	51.90	52.80	53.55	54.10	50.5	55.6
20	0	50.90	51.90	52.80	53.55	54.10	50.4	54.6

the young adults in this study is −0.72 for the men and −0.76 for the women. For the correlation with relative tibia length, the values are —0.67 and —0.64. It should also be remembered that the arms of an infant are nearer their adult lengths than are the legs and that the changes in relative lengths during growth will be less for the humerus and radius than for the femur and tibia.

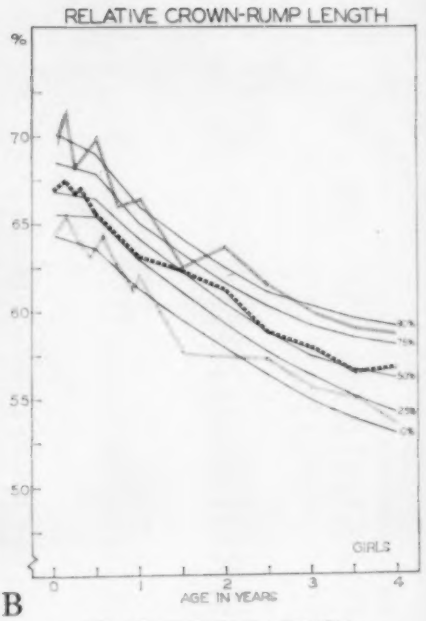
5. Since the segmental proportions appear to be well differentiated for the infant, it seems logical to assume that they will not change their comparative levels during growth and that the relative lengths of an individual at successive ages might be expected to remain in much the same relation to the percentile zones or channels at one age as another. At the extremes of the range for any of the relative lengths this is usually the case, i. e., the very short-legged infant will not become a very long-legged child or vice versa. However, a fairly large percentage of the group will show some shifting of their percentile position in some or all of the linear segments during infancy and/or childhood and/or adolescence.

Comment

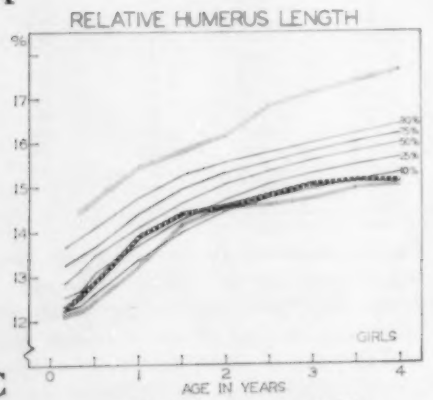
Although the data from which this study has evolved have been collected from the records of over 200 children, it is obvious from the manner in which the data were collected that there are a limited number of people whose records include measurements of the long bones from birth through adolescence to the end of long-bone growth. Of the 94 young men and women in this study, 31 have had seriatim measurements from infancy; 26 have had such measurements from the age of 4 years on, and


LENGTH
HEIGHT
CM
100
90
80
70
60
50
90%
50%
10%
90%
75%
50%
25%
10%
GIRLS
0
1
2
3
4
AGE IN YEARS

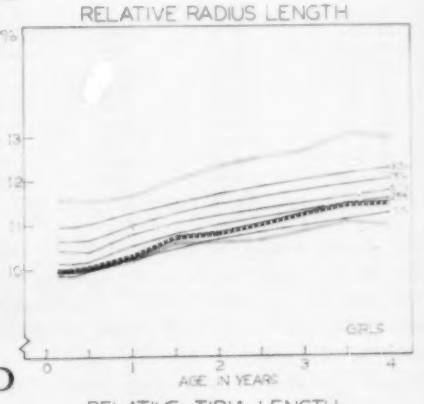
A


RELATIVE CROWN-RUMP LENGTH
%
70
65
60
55
50
GIRLS
0
1
2
3
4
AGE IN YEARS

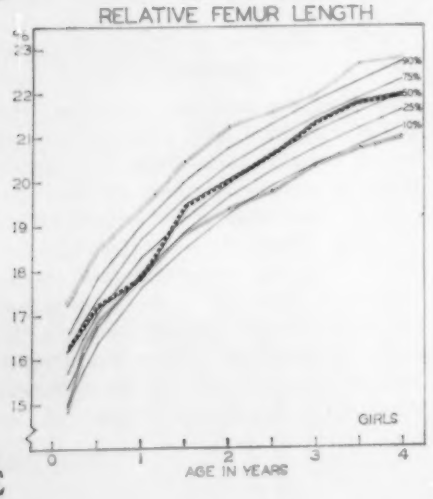
B


RELATIVE HUMERUS LENGTH
%
17
16
15
14
13
12
GIRLS
0
1
2
3
4
AGE IN YEARS

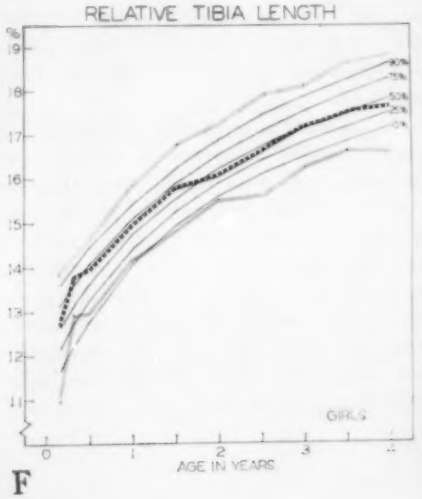
C


RELATIVE RADIUS LENGTH
%
13
12
11
10
GIRLS
0
1
2
3
4
AGE IN YEARS

D


RELATIVE FEMUR LENGTH
%
23
22
21
20
19
18
17
16
15
90%
75%
50%
25%
10%
GIRLS
0
1
2
3
4
AGE IN YEARS

E


RELATIVE TIBIA LENGTH
%
19
18
17
16
15
14
13
12
11
90%
75%
50%
25%
10%
GIRLS
0
1
2
3
AGE IN YEARS

F

37 had their initial long-bone measurements between the ages of 4 and 8 years.

The data on these 94 young men and women are the basis for this discussion. An effort will be made to present this material from three different aspects. One is the obvious longitudinal approach: Were the segmental proportions of the infant or the young child of the same magnitude within that age group as they were when compared with the other young adults at the end of long-bone growth? Or, if the relative length of one segment, such as the femur, became progressively greater in percentile rank during adolescence, did the bones of the arm and the lower leg also shift their percentile position?

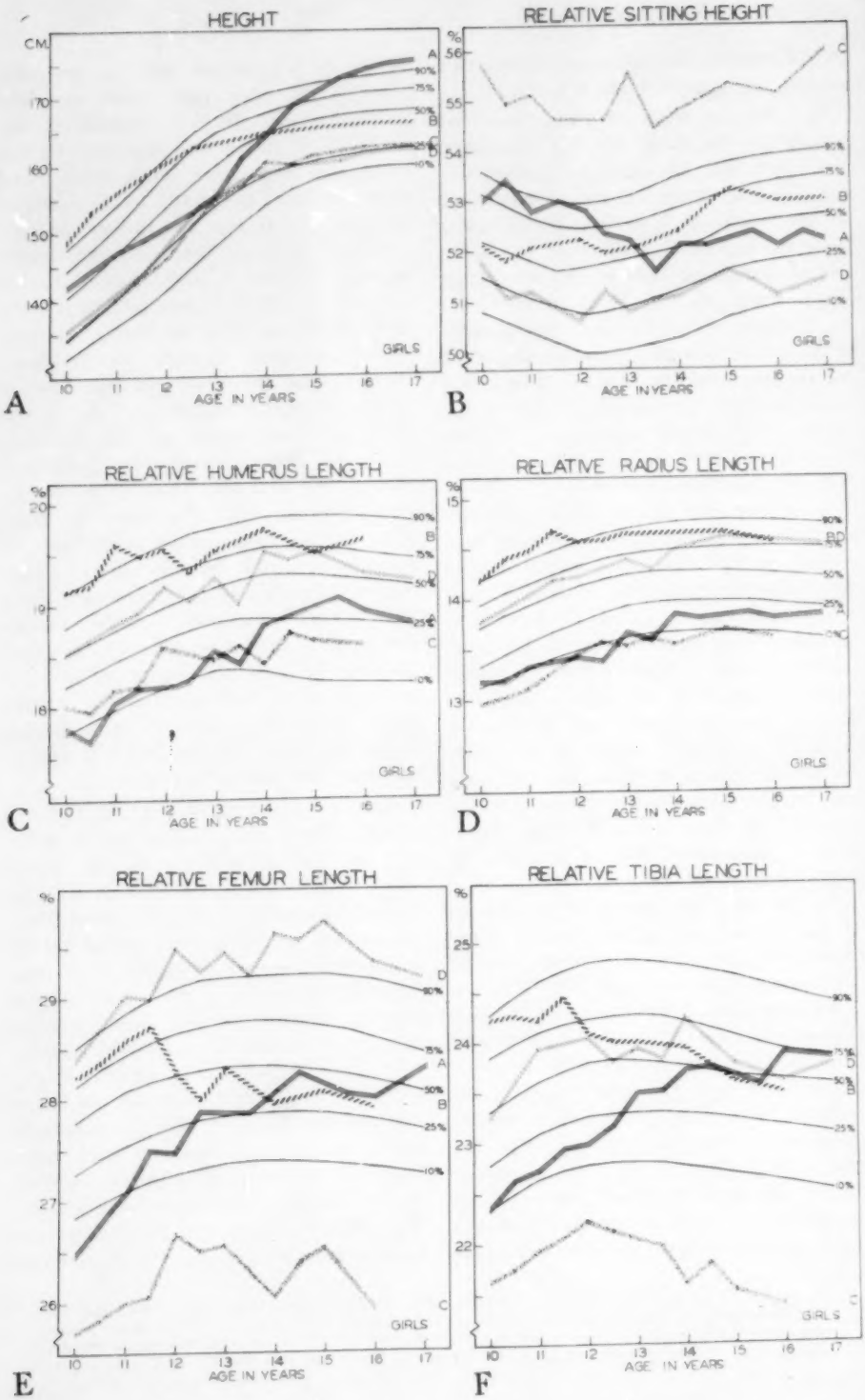
An attempt will also be made to demonstrate the variability in the segmental proportions in the young men and women in this study. For example, is there a commonly recurring or "normal" pattern of segmental proportions? Are the proximal segments more frequently of comparable relative length than the upper and lower arm or upper and lower leg? Within the range of variability observed in this study are the extremely short or the extremely long relative segmental lengths easily recognized by the observer, or are these differences in proportions only of mathematical significance?

Finally, are the segmental proportions of the 20 pairs of siblings in this group more alike than those of randomly selected pairs of unrelated boys and girls?

An Appraisal of the Changes in Linear Proportions That Occurred in 94 Boys and Girls as They Grew into Young Adults.—Of 31 boys and girls whose records are complete from within the first year of life to late adolescence and early adult life, less than a third (9, or 29.0%) had no change in the percentile levels for any of their relative bone lengths or sitting height during this time period. A few individuals (3, or 9.7%) had no shifts in percentile channels till adolescence, when segmental proportions changed quite markedly. Seven, or 22.6% of this group had fairly marked changes in proportions during infancy and early childhood, arbitrarily set as ending at 4 years of age, but no further shift in percentile levels for their relative lengths through childhood or adolescence. The other 12 persons (38.7%) also had infancy and early childhood shifts in levels, but these shifts continued through the childhood years and/or the adolescent years for at least some of the segments. Thus, of this group of 31 people, the percentile positions of early infancy were not maintained through the first four years of life in 19, or 61.3%. In only nine instances, three boys and six girls, were proportions in the same percentile zones in infancy and at the end of adolescence when long-bone growth was complete. Slight further change in segmental proportions may occur in the early adult years since trunk length will continue to increase after the completion of long-bone growth, but these changes will be minimal in degree and will not significantly alter the body build.

As might be expected from the previous group, when 4 years is used as the initial age for consideration of the 57 people whose records are complete from that age through adolescence, the distribution into groups will be significantly altered by the omission of the infancy period. Now there were 29 persons, or 51%, whose relative lengths remained in the same percentile zones from 4 years of age through adolescence; 14 (24%) whose relative lengths changed during adolescence but not before that period; 9 (16%) who had significant shifts in percentile levels toward either longer or shorter relative lengths for only one of the four long bones, and 5 (9%) whose relative lengths changed during childhood and usually continued to change dur-

Fig. 2.—The data for changes in height (*A*), relative crown-rump length (*B*), and the relative lengths of the humerus (*C*), radius (*D*), femur (*E*) and tibia (*F*) of three young girls are graphed against chronological age from birth to 4 years. The percentile values for the standards of reference in use at the Child Research Council are also shown.


HEIGHT
CM.
170
160
150
140
A
90%
75%
50%
B
25%
D
10%
GIRLS
10 11 12 13 14 15 16 17
AGE IN YEARS
A
RELATIVE SITTING HEIGHT
%
56
55
54
53
52
51
50
C
90%
75%
B
50%
A
25%
D
10%
GIRLS
10 11 12 13 14 15 16 17
AGE IN YEARS
B
RELATIVE HUMERUS LENGTH
%
20
19
18
90%
B
75%
D
50%
25%
C
10%
GIRLS
10 11 12 13 14 15 16 17
AGE IN YEARS
C
RELATIVE RADIUS LENGTH
%
15
14
13
90%
B D
75%
50%
25%
A
10%
C
GIRLS
10 11 12 13 14 15 16 17
AGE IN YEARS
D
RELATIVE FEMUR LENGTH
%
29
28
27
26
D
90%
75%
A
50%
B
25%
10%
C
GIRLS
10 11 12 13 14 15 16 17
AGE IN YEARS
E
RELATIVE TIBIA LENGTH
%
25
24
23
22
90%
75%
D
50%
B
25%
10%
C
GIRLS
10 11 12 13 14 15 16 17
AGE IN YEARS
F

ing adolescence. Thus, for about half the group, segmental proportions, in relation to the percentile zones at the age of 4 years, were unchanged at subsequent ages.

Using these same classifications for the 37 persons whose initial roentgenograms of the long bones were taken between the ages of 4 and 8 years, 26, or 70%, showed no shift in percentile levels during the time of study; 5 showed shifts in only one segment; 4 had no change in level for the relative lengths until adolescence, and 2 had continuing shifts in percentile zones for some of the segments through childhood and adolescence.

In summarizing the graphs of the 94 persons whose measurements of relative lengths in sitting height, humerus, radius, femur, and tibia lengths have been continuous from infancy, from 4 years of age or from before 8 years of age to the end of long-bone growth, the changes in percentile level for any or all segments seem to be related to developmental periods. The infancy and early childhood years seem to be the age period where the percentile levels are frequently changing to longer or shorter channels, the percentile position for any of the linear segmental proportions are usually the same through the childhood years, and an individual's segmental proportions may change considerably during adolescence. This would appear to be further verification of the observation that "three age periods seem to describe best the linear growth processes—an infancy period, a childhood period, and the adolescent years." [2]

Variations in Body Form Produced by Differences in Segmental Proportions.—In Figure 3 are shown the data for height, relative sitting height, and the relative bone lengths for four girls from 10 years of age to the end of long-bone growth. In Figure 3*A*, Girl A becomes a tall young woman; the tall Girl B becomes a less than average height young adult, and Girls C and D are of essentially the same height (at the 25th percentile) from 10 years on. Segmental proportions vary greatly, however, as is seen in Figure 3 (*B-F*). Girl C is now seen as very long-trunked and short-legged, while Girl D is short-trunked with a very long relative femur length. The relative leg bone lengths of Girl A becomes progressively greater in percentile position during adolescence, while relative sitting height becomes less. Photographs of these four young women, taken to the same scale, are shown in Figure 4. The differences in segmental proportions, so well seen in the graphs, are less apparent in these photographs since few of us are sufficiently well trained to judge lengths in terms of per cent of height.

Of the 94 young adults under discussion, 47 are men and 47 are women. Only their final or young adult data will be considered in the balance of this discussion. The mean values and the standard deviation for their height and sitting height and for their relative sitting height, and the relative lengths of the humerus, radius, femur, and tibia are as follows:

	Men		Women	
	Mean	S.D.	Mean	S.D.
Height, cm.	180.12	5.43	166.64	6.12
in.	70.91	2.14	65.61	2.41
Sitting height, cm.	93.51	2.93	87.78	3.25
in.	36.81	1.15	34.56	1.28
Relative lengths %				
Sitting height	51.91	1.04	52.68	1.07
Humerus	19.60	0.59	19.10	0.63
Radius	14.79	0.48	14.20	0.43
Femur	28.53	0.72	28.09	0.58
Tibia	23.98	0.73	23.40	0.72

To facilitate classifications and comparisons, the measurements for each individual were then converted into standardized scores by use of the equation $K=\frac{X-M}{\sigma}$ (standardized score = deviation from the mean divided by the standard deviation).

Fig. 3.—The data for changes in height (*A*), relative sitting height (*B*), and the relative lengths of the humerus (*C*), radius (*D*), femur (*E*) and tibia (*F*) of four young women are graphed against chronological age from 10 years of age through adolescence to the end of long-bone growth. The percentile values for the standards of reference in use at the Child Research Council are also shown.

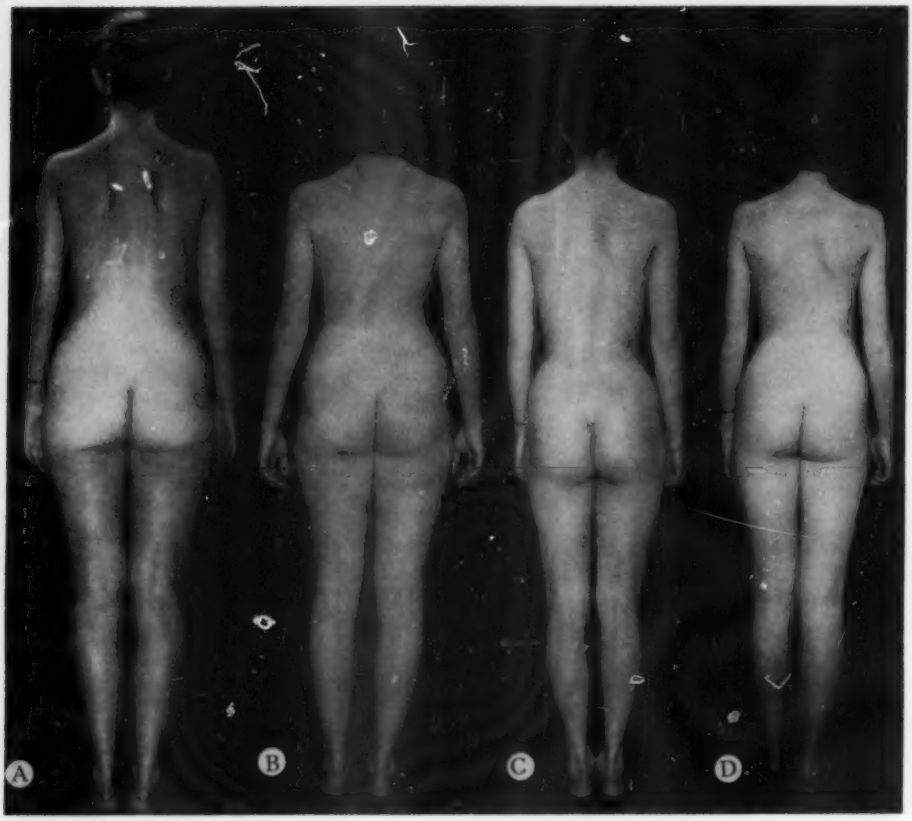


Fig. 4.—Photographs to scale of the four young women whose measurements of height and relative segmental lengths are graphed in Figure 3. The letters *A*, *B*, *C*, and *D* correspond to the letters for the individual curves in Figure 3.

Each value could then be described as long, moderately long, average, moderately short, or short by arbitrarily setting up zones of distribution. Standardized scores of 0 ± 0.5 were considered average (about 38% of the group); values between $+0.5$ and $+1.2$ were called moderately long (19%); values of $+1.2$ and above were called long (12%), and similarly those values below -1.2 were called short and those between —0.5 and -1.2 moderately short.

In common with our concept of "average height" and "average weight," it does not seem unreasonable to think of a body form of "average linear proportions." It might seem as though an individual whose relative lengths are average for the trunk, the bones of the upper and lower arm, and the upper and lower leg would be the commonly occurring body form and that deviations would be limited to a few people whose proportions were distinctly unusual. That it not borne out in this study. In only two instances, a moderately tall man and a moderately short woman, are the four segments of the extremities all within $\pm 0.5\sigma$ from the mean and in both the relative sitting height is between $+0.5\sigma$ and $+1.0\sigma$. By using the limits of $\pm 1.0\sigma$ as the standard for "average segmental proportions," there are 18 people, 10 men and 8 women, in that category. Two of these 18 people are tall; three are moderately tall; six are

of average height; three are moderately short, and four are short.

In spite of the variations in both sign and size of the standardized scores for the relative lengths, some other classifications are possible. Using again the fivefold classification of long, moderately long, average, moderately short and short, certain combinations of height and the relative lengths seem worth describing.

In the 12 young people who fall into the tall group (at or above 186.6 cm. for men and 174.0 cm. for women), all but one have average or above average relative length femurs and tibias. However, the femur and the tibia are usually not both in the long group; either may be long, moderately long, or average. In five the femur is relatively the longer; in four the tibia is relatively the longer, and in three the two bones are of approximately equal relative lengths. The relative lengths of the arm bones of these 12 are much more variable, with combinations as different as a moderately long humerus and a short radius, an average-length humerus, and a moderately long radius, long humerus, and a long radius.

In the 12 short young men and women (at or below 173.6 cm. and 159.3 cm. respectively), the ranges for relative lengths of the long bones of the leg are greater and include no short femurs and but three short tibias. The distribution is not weighted as heavily toward short legs for this group as it is toward long legs for the tall people. The relative length of the arm bones appear to be little related to the stature of the short people, although it is noted that only one woman has a long humerus and one man a long radius. The wide range of variation of relative femur length with respect to height can be seen in Figure 5. In this graph it is obvious that femurs of near average relative length are found in people of markedly different total heights.

As might be expected from Figure 5, the coefficients of correlation between height

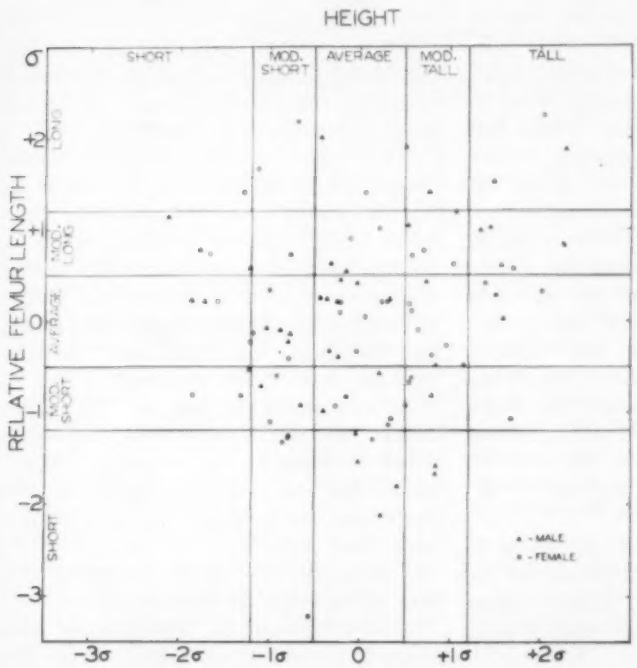


Fig. 5.—Standardized scores for relative femur lengths are graphed against standardized scores for height for the 47 young men and the 47 young women in the Child Research Council whose data have been used in this study of segmental proportions.

and the relative lengths of the bones of the extremities are essentially zero. They are as follows:

Coefficients of Correlation

	Men	Women
	r	*r*
Height: Relative humerus length	+0.04	+0.09
Height: Relative radius length	+0.03	0.00
Height: Relative femur length	+0.12	+0.14
Height: Relative tibia length	+0.43	+0.19

Since the lengths of the femur and the tibia are significant parts of the measurement of total height, the calculation of relative bone length with this height measurement as the divisor in the equation may well be responsible for the slightly higher coefficients of correlation between height and the relative lengths of the leg bones, especially for the tibia in the young men.

Of probably more importance in classifying body build than the relationship of the relative bone lengths to height is the comparison of one relative bone length to another. If other criteria than height are the basis for sorting these young adults into groups, some of the combinations of lengths are more clear-cut. As a rule, persons with long femurs will not have moderately short or short tibias, humeruses, or radiuses, and those with short femurs will not have moderately long or long relative lengths in the other segments of the extremities. These same generalizations can be made for those persons with long and short tibias, humeruses, and radiuses. There are exceptions, however, and one such is a young man of average height with a short femur, an average tibia, a long humerus, a long radius, and a moderately long sitting height. Few persons will show this much variation, but it cannot be presumed that the standardized scores of the relative lengths of the four major segments of the extremities will be the same.

One might reasonably expect the proximal and distal segments of the arm or the leg to be "balanced" as to relative lengths because of their close relationship to each other developmentally and functionally. Further, the easily recognized clinical picture of rhizomelic disproportions (foreshortened proximal or root segments) in achrondroplasia suggests that the humerus and femur may have common responses to certain stimuli during fetal life. We might, therefore, reasonably expect the proximal segments of the extremities to be of comparable relative lengths in normal as well as abnormal growth. Is it also reasonable to expect a closer relationship between the relative lengths of the distal segments (radius and tibia) in young adult life than between a proximal arm bone and distal leg bone (humerus and tibia) or between the radius and femur? The coefficients of correlation between the relative bone lengths in various combinations are as follows:

Coefficients of Correlation
Between Relative Lengths

	Men	Women
	r	*r*
Radius: Tibia	+0.60	+0.57
Humerus: Femur	+0.53	+0.38
Humerus: Radius	+0.44	+0.53
Femur: Tibia	+0.40	+0.46
Humerus: Tibia	+0.38	+0.19
Radius: Femur	+0.32	+0.25

While not high enough to be of much significance, it is evident that the two lowest values for both sexes are those between the humerus:tibia and the radius:femur.

What, then, are the commonly found relative length relationships that occur in these 94 people? The differences in magnitude of the relative lengths of each of the four segments of the extremities having been minimized by converting the values for relative lengths into standardized scores, the "alikeness" or "difference" between them becomes readily apparent.

In addition to the two persons of so-called "average" proportions previously noted, there are four more who had "alike" scores for all four segments—two with short, one with long, and one with moderately short segments. This small group of six shows the most easily recognized pattern of segmental proportions.

Another group that appeared to have much in common is made up of 30 persons

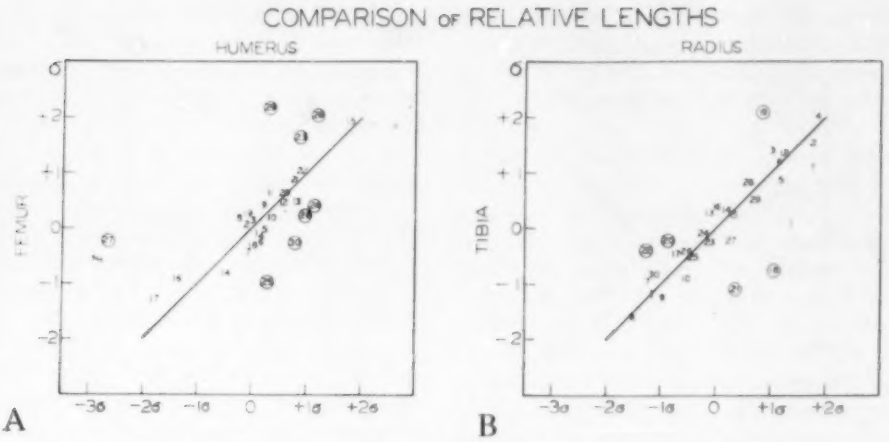


Fig. 6.—Standardized scores for the relative lengths of the proximal segments of the extremities (humerus and femur) graphed against each other in *A* and for the relative lengths of the distal segments (radius and tibia) graphed against each other in *B* for 30 of the 94 young adults in this study. The values for each person have been given the same number on both graphs. Circled numbers designate the individuals in whom either proximal or distal segments are of "different" relative lengths while their proximal or distal segments are "alike" on the opposite graph.

with nearly equal standardized scores for both proximal long bones and/or both distal long bones. These are illustrated in Figure 6, where, in *A*, the score for the relative length of the humerus is graphed against the score for the relative length of the femur with a number. Each number represents an individual, so, in *B*, the same number is used to graph the score for the radius against the score for the tibia. Thus it is apparent that while the humerus and femur are of average relative length for both the young women numbered 1 and 2, the radius and tibia are moderately short in Subject 1 and long in Subject 2. The proximal segments are longer than the distal in half the group, and the distal segments are longer than the proximal in the other half. For 17 of this group (numbered 1-17), the proximal or root segments are "alike" and the distal segments are also "alike." In the other 13, only proximal segments are alike in 5 (numbered 18 through 22), with differences in the distal segments as great, for example, as a short radius and an average length tibia. The "different" segments in Figure 6*B* are circled to emphasize the difference. The other eight persons (numbered 23-30) have distal segments alike, but there are differences in the proximal segments. The "different" segments in Figure 6*A* are also circled.

The next most commonly found pattern of similarity in linear segmental proportions is found in 23 persons whose arm bones are "alike" and/or whose leg bones are "alike." These are illustrated in Figure 7, where the standardized scores for the relative lengths of the humerus and radius are graphed against each other in *A*, and the scores for the femur and tibia are shown in *B*. The arm bones are alike and the leg bones different in 11 persons (numbers 37-47, circled on Figure 7*B*), and the arm bones are different and the leg bones alike in 6 persons (numbers 48-53, circled in Figure 7*A*). The arm bones are alike and the leg bones are also alike in the other 6 (numbers 31-36). The leg bones are relatively longer than the arm bones in 11 persons, and the arm bones are relatively the longer in 12.

In 21 persons there are three of the four bones with nearly equal standardized scores, while the fourth is a variant. The variable

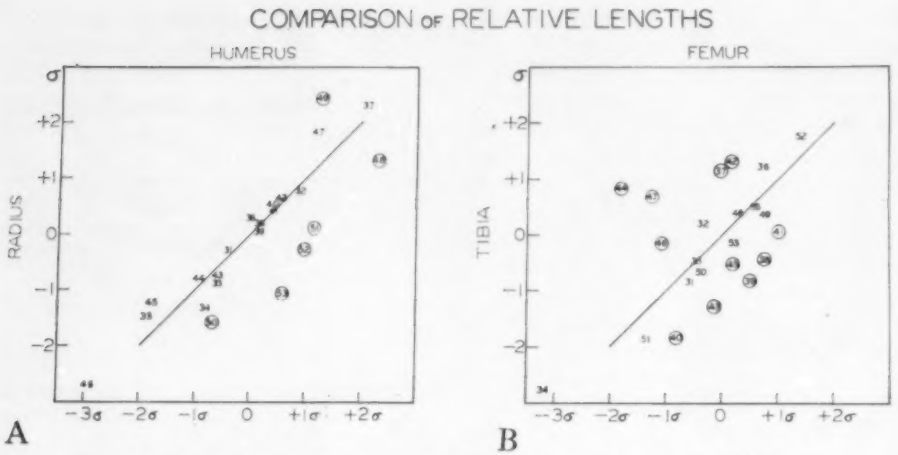


Fig. 7.—Standardized scores for the relative lengths of the upper and lower arm (humerus and radius) graphed against each other in *A* and for the relative lengths of the upper and lower leg (femur and tibia) graphed against each other in *B* for 23 of the 94 young adults in this study. The values for each person have been given the same number on both graphs. Circled numbers designate the individuals in whom the segments of either the arm or the leg are of "different" relative lengths while the segments of either the arm or the leg are "alike" on the opposite graph.

bone, either longer or shorter than the others, is the femur in nine instances, the tibia in six, the radius in four, and the humerus in two. It would be possible, of course, to put each of these individuals in both the preceding groups, since either the two proximal or the two distal segments will be alike, as will either the two segments of either the arm or the leg. They differ from the preceding groups, however, in that only the one segment is different from the others.

There remains a group of 14 persons with so much variability in both sign and size of their scores that classification seems impossible.

Thus the relative bone lengths of this group of 94 young adults indicate not only inter-person differences in the standardized scores for the relative lengths of the four segments of the extremities but considerable intra-person variability. Some broad classifications of linear proportions are possible, but these are of limited value in anticipating the probable proportions of a given individual from any one measurement of size.

Segmental Proportions of Siblings.—The comparisons that are made between members of the same family are frequently those of personality traits, of facial configuration, or of body size in terms of height and weight. If comparisons of body build are made, independent of size, they are likely to involve measurements of widths and depths, such as shoulder breadth or hip width. Few of us have sufficiently well-trained eyes to be able to recognize differences of 1% or 2% of height, especially in persons of markedly different statures.

An investigation of the linear relative segmental lengths in siblings might support a hypothesis that these proportions are genetically determined or, an opposite hypothesis, that similarity in the relative lengths of one or more segments are chance occurrences in an adult population. To test these hypotheses, data are available on 20 pairs of siblings who are now young adults. These are made up of eight pairs of brothers, six pairs of sisters, and six pairs of brothers and sisters.

The usually accepted statistical methods for testing variance and concordance were

employed to try to demonstrate that siblings are more like each other in the relative lengths of their humeruses, radiuses, femurs, and tibias than are young adults in general. None of these tests were successful at high enough levels of confidence to be noteworthy. Even if we assume that relative bone lengths might be gene determined, those siblings who did not have in common the gene for a certain component, e. g., a relatively long femur, might vary greatly in their relative femur length. Such variation could, in statistical determinations, tend to obscure those siblings who did have nearly the same relative femur lengths. Since it would be unrealistic to expect all the pairs to be alike in the relative lengths of even one segment, it is doubtful if statistical proof of similarity in the linear segmental proportions of members of the same family will be forthcoming from the study of one generation.

Nevertheless, in studying these data, one cannot escape the conviction that the proportions of siblings are often alike. Of the 94 young adults, the 2 whose relative arm bone lengths are the longest are brother and sister; 2 pairs of brothers are 4 of the 5 boys with the longest leg bones; 2 sisters have the shortest of the relative tibia lengths, etc. The coefficients of correlation, calculated from the standardized scores, for the sibling pairs and for pairs of nonsiblings selected at random are as follows:

	Coefficients of Correlation (r)	
	Siblings, 20 Pairs x=Younger y=Older	Nonsiblings, 47 Pairs Selected at Random
Relative humerus length	+0.33	+0.13
Relative radius length	+0.49	+0.10
Relative femur length	+0.46	−0.05
Relative tibia length	+0.73	+0.12
Relative sitting height	+0.46	−0.06

For purposes of calculation, the distributions of the standardized scores for the young men and women were shifted from a mean of 0 to a mean of 10 to eliminate the negative values in the original distribution. It is evident that the calculated values for r with the nonsibling pairs are essentially zero. The values for r with the sibling pairs, while not high enough to be interpreted as evidence of sibling similarities, are certainly suggestive of such an interpretation.

The comparison of the relative bone lengths and relative sitting height between each pair of siblings was also attempted in terms of percentile levels. In determining these percentile levels, the standardized scores for the 94 young people were incorporated into ogives. It was then possible to translate each point on the double-S-shaped ogive curve into a corresponding percentile value for each of the segmental lengths. In general, deviations from the mean of more than $+1.5\sigma$ were above the

TABLE 5.—*Percentile Levels for Relative Lengths*

Sibling Pair	Sex	Humerus	Radius	Femur	Tibia	Sitting Height
A	F	89	46	12	<5	83
	F	18	8	<5	<5	>95
B	F	>95	80	62	66	28
	F	33	65	14	60	86
C	F	25	45	28	25	80
	F	25	51	37	17	69
D	F	24	70	9	20	90
	F	35	32	16	54	95
E	F	18	<5	37	26	66
	F	76	44	75	80	16
F	F	29	30	31	17	90
	F	53	40	80	50	71
G	M	34	35	31	20	80
	M	55	19	66	10	43
H	M	23	34	32	43	76
	M	11	10	<5	9	>95
I	M	30	42	86	40	30
	M	71	22	75	43	12
J	M	56	59	86	34	41
	M	60	90	88	70	26
K	M	28	84	92	66	33
	M	<5	64	25	43	86
L	M	>95	81	57	88	10
	M	44	50	56	94	41
M	M	38	50	60	>95	14
	M	87	81	85	>95	<5
N	M	83	>95	>95	>95	<5
	M	61	23	93	83	21
O	M	5	47	21	30	82
	F	<5	5	35	33	94
P	M	92	>95	80	66	11
	F	38	78	>95	71	22
Q	M	51	53	72	20	89
	F	83	75	73	32	73
R	F	38	95	52	93	22
	M	63	61	21	62	72
S	M	92	>95	10	75	60
	F	>95	>95	50	87	35
T	M	60	95	76	86	30
	F	81	70	37	60	66

95th percentile and those of more than -1.5σ were below the 5th percentile. No attempt was made to define percentiles beyond these levels. The data for the 20 pairs of siblings are given in Table 5, with the younger member of each pair listed first. The segments that are at about the same percentile level in each pair are set off in bold-face type. Here, approximately a half-quartile difference or not over 12 percentiles were arbitrarily set as the limits for "alike" proportions.

It is evident that none of the pairs have relative lengths of the same proportions for all four long bones of the extremities and for relative sitting height, although the two sisters of Pair C approach this similarity. It is also evident that of the 100 pairs of measurements, there are 32 that are considered alike. These are not equally distributed in the five columns since the relative lengths of the tibia are alike in 10 of the 20 pairs of siblings, of the femur in 7 pairs, the humerus in 6 pairs, the radius in 4 pairs, and relative sitting heights are alike in 5 pairs. It is also interesting that the differences between percentile levels for the relative lengths in each pair exceed 50 percentiles only once for the radius and tibia, twice for the femur, four times for the humerus, and three times for relative sitting height. Another observation is that the differences in the segmental proportions of the two brothers in Pair H are of about the same magnitude for each segment, the older brother being relatively shorter-boned and longer-trunked than the younger.

It would seem, therefore, from both the coefficients of correlation and the figures in Table 5 that the relative lengths of at least one of the linear segments of the body might more often be alike in siblings than in randomly selected pairs of nonsiblings.

Summary

As a part of the study of the physical growth of the subjects in the Child Research Council study series, the linear proportions of the body segments have been investigated. The bone lengths of the humerus, radius, femur, and tibia on roentgenograms of the left extremities have been considered as equivalents of the lengths of the upper and lower arm and the upper and lower leg. These lengths, when expressed as per cent of height, have been termed "relative lengths" in this discussion. Similarly the measurements of crown-rump length and sitting height have been converted into "relative crown-rump length" and "relative sitting height" by dividing the measurement by body length or height.

Standards of reference for percentile levels for the relative lengths from infancy to young adult life have been derived from the seriatim measurements of over 200 persons. Since the rate of growth in length of the major long bones of the extremities is greater than the rate of growth in height, it is obvious that the values for relative lengths of these bones will be progressively larger values during childhood and adolescence. At the same time, sitting height will be a progressively smaller per cent of height during these years. Thus the changing relative lengths of the segments of the extremities are best described in relation to the percentile levels at each successive age. Only a few persons will have relative lengths that remain at the same percentile level throughout their growing years. In general the infancy period and the adolescent years are the times when shifts to higher or lower percentile levels occur. These changes in proportions to relatively longer or shorter segments are rarely of extreme magnitude, i. e., the very short-legged infant may become an adolescent with relative leg lengths near the median for the group but he is not likely to become a relatively long-legged adolescent or young adult. During the childhood years, from about 4 years of age till the onset of adolescence, percentile positions are usually quite stable and only minor deviations in percentile positions are observed.

The linear proportions of 94 young adults show not only a great deal of variation be-

tween individuals but a wide range of variation in the comparative relative lengths of the long bones of the extremities and of relative sitting height in the same person. The computed standardized scores were used to set up five zones of distribution—average, moderately long, moderately short, long, and short. Using these criteria, only 2 of the 94 persons had "average" relative bone lengths. It was common for the relative bone lengths in an individual to be spread over three of the five zones but uncommon for the proportions of one person to include both a very long and a very short relative bone length.

Within this group of 94 young adults some classification of segmental proportions that were "alike" was possible. In frequency these were as follows:

1. Alike proximal segments (humerus and femur) and/or alike distal segments (radius and tibia)—32%
2. Alike segments of the arm (humerus and and radius) and/or alike segments of the leg (femur and tibia)—25%
3. Three of the four segments alike—22%
4. All four segments alike—6%
5. Unclassified—15%

The reciprocal relationship between relative leg bone lengths and relative sitting height was plainly evident in these data. It was also evident that individuals of the same height often varied greatly in their segmental proportions and that there was no correlation between the relative lengths of any of the long bones and total height.

Included in this group of 94 young adults are 20 pairs of siblings. The correlation coefficients between the younger and the older members of each family for the standardized scores of the relative bone lengths and for relative sitting height range from +0.33 to +0.73. In contrast, the values for r in the 47 randomly selected pairs ranged from −0.06 to +0.13. The computed percentile levels for the relative lengths for the sibling pairs are presented. The assumption that the segmental proportions in siblings will be alike more often than in nonsiblings would appear to be warranted.

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A Genetic Profile of Infantile Amaurotic Family Idiocy

Statistical Evaluation of One Hundred Thirty-One Patients

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Since the initial descriptions by Tay [1] (1881) and Sachs [2] (1887), an estimated 500 separate cases of infantile amaurotic family idiocy (IAFI) have been cited in published medical reports. These formal descriptions, reflecting the individual interests of the authors, have dwelled upon varying facets of the disease, with the greatest emphasis placed upon pathologic observations. In 1933, Slome [3] prepared the first comprehensive genetic analysis of the disorder, based upon a survey of the 135 adequately described cases available in the medical literature to that date. A comparable study by Ktenidès [4] incorporated the case reports published between the years 1933 and 1949, and included an additional 99 instances of the disease. Further assessment of the genetic background of IAFI became available when Kozinn and associates [5] examined the death certificates in New York City for the years 1944 to 1954 and were able to personally interview the immediate families of 43 established cases of IAFI. By extrapolation these authors postulated the carrier heterozygosity in the population. A further study of the carrier rate of this disorder in Israel was recently published by Goldschmidt and associates.[6]

A reliable analysis of the characteristics of IAFI requires a body of information derived from each family, more extensive than that presently available. Furthermore, a considerable number of cases is needed to insure statistical validity of the extracted information. In acknowledgement of this, a questionnaire including 112 points of inquiry was prepared in 1954 and distributed to the families of children with central nervous system lipidoses. Through the help of the National Tay-Sachs' Association and cooperating physicians a total of 144 cases became available (Table 1). It is believed that none of these patients has been included in previous publications except in terms of pathologic, biochemical, and anthropometric studies originating from this laboratory. The present report offers a brief statistical analysis of the data derived from the questionnaires, often augmented by clinical observations gathered during hospitalization.

A. Compilation and Classification of Cases

The problem of diagnostic reliability is reduced by the stereotypic clinical nature of IAFI and the availability of autopsy confirmation in 27 of the cases. Where pathologic studies were not feasible or where the

TABLE 1.—*Studied Cases of Central Nervous System Lipidoses of Infancy and Childhood*

1. Infantile amaurotic family idiocy		131 *
Male	76	
Female	55	
2. Niemann-Pick's disease, with central nervous system involvement		8
Male	4	
Female	4	
3. Juvenile amaurotic idiocy (Spielmeyer-Vogt's disease)		5
Male	2	
Female	3	
Total		144

* The number of evaluated cases in subsequent tables is often less than the total number of IAFI cases surveyed. Information on some aspects was incomplete, unavailable, or subject to doubt.

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patient is still alive, the critical triad of progressive idiocy, quadriparesis, and amaurosis accompanied by macular degeneration, was required of each case before acceptance. Enzymatic alterations of a characteristic nature, in serum and cerebrospinal fluid, were often used to reinforce the diagnosis.[7,8] Of the 144 cases included in this report, 131 were diagnosed as IAFI, 8 cases as Niemann-Pick's disease with central nervous system involvement (NPD), and 5 as juvenile amaurotic idiocy (JAI). Only with IAFI was the number of cases deemed sufficient for extensive statistical evaluation. Limited points of comparison, however, were made in reference to the two other included forms of nervous system lipidosis.

This compilation cannot be construed as indicating the comparative incidence of the three diseases since numerous biases were introduced. Initial interest was largely confined to IAFI. Subsequently, only a limited number of cases of the other central nervous system lipidoses was admitted, principally for purposes of comparative biochemical investigation.

In considering the IAFI group of 131 cases as a potentially homogeneous population, it became important to determine what control group was to be used for purposes of statistical comparison. If viewed against the general population, any potential differences might be due to critical determinants such as religion and nutrition. In order to establish a control series reasonably identical with the IAFI group in all major parameters, a system of paired siblings of same sex was utilized, differing only in not showing the specific disease. Even the utility of this system is open to question, since order of birth and other unmeasured conditioning factors are not assessed.[9]

No concerted effort has been made by previous observers to divide IAFI into major types, other than passing recognition of rare deviant varieties (e. g., absence of macular degeneration[10]). The unusually homogeneous clinical presentments and characteristics of this disease makes subdivision based only upon relative sequence or predominance of symptoms an artificial process. In the present study, a temporary separation (based upon religion) has been used to observe whether the afflicted children of non-Jewish background differ appreciably in disease development and other characteristics from patients of Jewish origin.

When the opportunity arose permitting extended clinical observation of the children with IAFI, it became apparent that distinctions of a qualitative nature emerged at reasonably predictable times during the course of the illness. Three phases of the disease which were based upon anthropometric, biochemical, and pathologic criteria,[11] are outlined in Table 2. During the course of this article, occasional reference will be made to, and comparisons drawn between, children succumbing during Phase I, II, or III of the disease. This is not to be taken as indicating a clinical separation but rather a notation of relative longevity. Thus, it is assumed that a child dying in Phase I of the disorder would have exhibited the changes exemplary of Phase II or of Phase III if survival were extended. The only purpose, therefore, of evaluating the

TABLE 2.—*Characteristics of Phases of Infantile Amaurotic Family Idiocy*

Phase I: (0-14 months of illness). Regression of development, apathy, hyperacusis; pneumoencephalograms show diffuse cerebral atrophy and secondary ventricular dilatation; serum glutamic oxalacetic acid (GO) transaminase and lactic acid dehydrogenase markedly elevated; cerebrospinal fluid aldolase, GO transaminase, and lactic acid dehydrogenase elevated. At autopsy, brain specimens show mild atrophy.
Phase II: (15-24 months of illness). Semivegetative existence, frequent abnormal movements, total blindness; pneumoencephalograms show a diminution of the formerly demonstrable ventricular enlargement; serum GO transaminase and lactic acid dehydrogenase moderately elevated; serum aldolase mildly elevated, coincident with appearance of skeletal muscle atrophy; cerebrospinal fluid enzyme changes as in Phase I, but less marked. At autopsy, brain specimens show normal or mildly increased brain weight.
Phase III: (more than 24 months of illness). Vegetative existence, hyperacusis minimal, rapidly increasing head circumference; pneumoencephalograms show a significant increase in supratentorial tissue volume and lateral ventricular diminution; serum GO transaminase mildly elevated; cerebrospinal fluid aldolase, lactic acid dehydrogenase, and GO transaminase mildly elevated. At autopsy, brain specimens show a marked supratentorial megalencephaly, with brain weights almost 50% above normal.

IAFI series in these terms is to determine whether associated factors (such as birth weight, sex, order of birth, etc.) are causally related to disease duration, the latter symbolized by the phase.

B. Nature of Pregnancy, Birth and Early Infancy

Questions relative to gestation and measurable factors in regard to birth were included in the scope of the questionnaire.

Age of the parents at time of conception has been considered a conditioning factor in the subsequent development of some neurologic disturbances of infancy.[12] The age of parents of children with IAFI was but rarely over 35 years. Less than 1% of the mothers were beyond the age of 40 when the afflicted child was born. About 9% of fathers were 40 years or older. No striking differences in parent age were evident with regard to subsequent length of survival of the afflicted child, as expressed in terms of disease phase. Mean ages of parents at the time of birth of children with IAFI, NPD, and JAI are contained in Table 3.

No major fertility problems were encountered, although 4% of the mothers described unsuccessful attempts at conception for periods up to six years. When contrasted to their efforts in instituting conception of the normal siblings, no disparities were evident.

Over 85% of mothers recorded a medically uncomplicated period of gestation. About 2% suffered from hyperemesis gravidarum during the first trimester of pregnancy and less than 4% developed transient hypertension and albuminuria during the third trimester. No infectious illnesses, other than occasional upper respiratory disturbances, were recounted. Except for a small number of pregnant mothers submitted to radiographic pelvimetry, there was no contact with x-radiation. Intrauterine movements were not diminished in those fetuses which were to reveal IAFI postnatally. In fact, three of the mothers commented that fetal activity was appreciably greater in their IAFI children than in their previous or subsequent normal off-spring. Length of gestation was within normal limits in 96 of the 109 cases of IAFI where obstetrical records were available. In 7% of the affected children, the birth was considered premature. The most abbreviated period of gestation was 34 weeks. Five children were born postmaturely (285-305 days). Furthermore, the ratio of spontaneous abortions to viable births (25:223) in this group was in accord with the proportion in the general obstetrical population.[13]

Duration and quality of labor were not abnormal. Not a single obstetrical or postdelivery clinical note expressed concern or suggested the possibility of infantile disease. Instrument delivery was often used (35%) but never because of fetal distress or uterine inertia. Two cesarean sections were performed, one because of placenta praevia and the other for undetermined reasons. One Kjelland version was required because of a transverse fetal position. Of the considered births 3.8% were breech presentations. The frequency data of the obstetrical factors mentioned above comply very closely with findings in the general maternity population.[13]

Birth weights of the children with subsequent IAFI were within the normal range

TABLE 3.—*Mean Ages of Parents at Time of Birth of Children with Central Nervous System Lipidoses*

	Father	% ≤40 Yr.	Mother	% ≤40 Yr.
Infantile amaurotic family idiocy				
Phase I *	34.9 yr.	20%	30.2 yr.	0%
Phase II †	32.1 yr.	8%	27.8 yr.	0%
Phase III ‡	31.5 yr.	5%	27.4 yr.	3%
Niemann - Pick's disease with central nervous system involvement	32.5 yr.	17%	30.3 yr.	0%
Juvenile amaurotic idiocy	36.4 yr.	20%	34.6 yr.	20%

* Children with IAFI succumbing within 14 months of onset of symptoms.

† Children with IAFI succumbing between 15 and 24 months after onset of symptoms.

‡ Children with IAFI succumbing beyond 24 months after onset of symptoms.

TABLE 4.—*Mean Birth Weights: Central Nervous System Lipidoses*

	Male	Female
Infantile amaurotic family idiocy *		
Phase I	7.6 lb.	7.0 lb.
Phase II	7.1 lb.	7.1 lb.
Phase III	7.5 lb.	7.1 lb.
Niemann-Pick's disease, with central nervous system involvement	6.8 lb.	6.2 lb.
Juvenile amaurotic idiocy	8.8 lb.	7.7 lb.

* See footnotes, Table 3.

(Table 4). The birth weights of those IAFI children subsequently to exhibit the more prolonged pattern of the disease were almost identical with the birth weights of the IAFI children with the shorter clinical course. Where possible, birth weights were also compared with those of normal siblings of the same sex. The children with latent IAFI tended to be slightly heavier at birth than their normal siblings, but the difference was very slight. Matched weights of 23 such pairs of siblings were collated. The weight of male IAFI newborn infants averaged 7.5 lb. (3,400 gm.) (normal male siblings, 7.2 lb. [3,265 gm.]). Female IAFI infants averaged 6.9 lb. (3,130 gm.) (normal female siblings, 6.7 lb. [3,040 gm.]). This negligible increase in weight had no statistical significance.

The birth weights of the JAI children were essentially normal. The children later to develop NPD, despite full-term gestational interval, were below normal birth weight (Table 4).

C. Onset and Initial Symptomatology

Appraisal of the clinical records of the hospitalized cases of IAFI often leads to some measure of confusion when attempting to establish an indisputable time of onset of the disorder. Parents were carefully questioned to determine the earliest age when pertinent symptoms commenced. The time of onset was often a measure of parental acuity rather than an objectively accurate and valid unfolding of some symptom complex. When the afflicted child was the first born, no point of comparison was available to the parents and hence subtle regression of development often went unnoticed. When the afflicted child was born after a previously unaffected sibling, a normal scale of maturation was available for comparison and hence detection of abnormality tended to occur at an earlier date. If, however, a child with IAFI had already been born into the family a heightened index of suspicion accompanied the early growth and activities of the newborn, and slightly deviant behavior was readily noticed by the apprehensive parents, who generally were aware of the familial nature of the disease. Thus, first-born children develop precursive symptoms, statistically, at a later date than subsequently born affected siblings. It is likely that the shortening of the latent interval is attributable to a parental sensitivity rather than a fundamental change in the velocity of the disorder with succeeding diseased siblings. Parental suspicion was not usually aroused until arrest or regression of development was noted. Abnormal movements of limbs, head, or eyes were occasionally the initial provocation for seeking medical advice. Progressive amaurosis, while an invariable component of the fully developed clinical complex of IAFI, was only rarely an inaugurating disability. It is possible, however, that the abnormal eye movements of a nystagmoid character may represent an

TABLE 5.—*Infantile Amaurotic Family Idiocy, First Abnormality Noted by Parents*

	No. *
1. Hyperacusis	82
2. Infant could not sit up	30
3. Abnormal head or limb movements	25
4. Inattentiveness	23
5. Generalized weakness	10
6. Infant could not hold head up	9
7. Irritability	7
8. Incoordination of limbs	7
9. Feet turned in	5
10. Infant could not turn over	4
11. Failing vision	4
12. Feeding difficulties	3
13. Constipation	2
14. Insomnia	1
15. Abnormal weight gain	1

* Initial abnormalities were often multiple; hence, total is greater than the 109 patients included in the above compilation

TABLE 6A.—*Onset, Age at Death, and Duration, 131 Patients with Infantile Amaurotic Family Idiocy*

Onset			Age at Death			Duration		
Months	Male	Female	Months	Male	Female	Months	Male	Female
0	2	1	0-5	0	0	0-5	2	0
1	1	0	6-10	3	0	6-10	3	4
2	3	2	11-15	2	2	11-15	10	6
3	13	4	16-20	9	9	16-20	11	8
4	5	8	21-25	11	8	21-25	7	8
5	12	9	26-30	10	8	26-30	8	3
6	13	13	31-35	6	1	31-35	6	6
7	12	7	36-40	5	6	36-40	4	4
8	9	3	41-45	5	3	41-45	3	2
9	3	3	46-50	3	4	46-50	0	0
10	2	5	51-55	0	0	51-55	1	0
11	1	0	56-60	2	0	56-60	1	0
No. of patients	76 *	55 †		56 *	41 †		56 *	41 †
Average	5.4 Mo.	5.8 Mo.		29.9 Mo.	28.9 Mo.		24.6 Mo.	23.5 Mo.
	5.6 Months			29.5 Months			24.1 Months	

* 20 male infants with IAFI in present series still alive.
† 14 female infants with IAFI in present series still alive.

attempt at compensation for failing vision. A significant number of parents intuitively felt concern because their child displayed an ill-defined lassitude or inattentiveness. Some parents brought their child to a physician because "the baby was too good." Constitutional abnormalities (feeding difficulties, diarrhea, etc.) were only rarely the motivation for medical consultation. The presenting symptoms and signs of IAFI exhibited by non-Jewish and Jewish infants with the disease were basically the same (Table 5).

Every one of the 109 cases of IAFI was clinically apparent before the 11th month of life, the age of initial recognition averaging 5.6 months (Table 6A).

The initial symptoms in the eight cases of NPD with central nervous system involvement tended to arise at an earlier age (4.2 months) than in IAFI. In addition to many of the abnormalities associated with IAFI (viz., hyperacusis, failure in development) signs such as abdominal enlargement were also recorded. The five cases of JAI were ostensibly normal until an average age of 7.2 years, when failing vision usually constituted the first noted irregularity (Table 7).

While it is of value to recognize the nature of preliminary symptoms and signs, these data should not be viewed as equivalent to the true onset of the disorder. Case 6 is illustrative of the indisputable time lag between the pathologic and clinical emergence of IAFI. A previous sibling had died of IAFI, and as a result the infant was submitted to periodic examinations. At the

TABLE 6B.—*Duration of Life Following First Symptoms (IAFI) in Relation to Sex*

	% Dying in Phase		
	I	II	III
Male	24.0	33.3	42.6
Female	19.5	39.0	41.5
Both sexes	22.1	35.8	42.1

TABLE 7.—*Niemann—Pick's Disease, First Abnormality Noted by Parents*

	No. *
1. Abdominal enlargement	3
2. Generalized weakness	3
3. Vomiting, feeding difficulties	2
4. Failure to sit	1
5. Hyperacusis	1
6. Irritability	1
7. Failure to hold head up	1
8. Abnormal eye movements	1

* Initial abnormalities were often multiple; hence, total is greater than the 8 patients included in the above compilation.

age of 7 months, bilateral macular degeneration was visualized. At this time, no other abnormalities were found. At age 10 months, the child had an upper respiratory infection associated with fever. After this episode the infant regressed, displayed periodic convulsions and exhibited visual impairment. The macular degeneration in this patient undoubtedly represented an intraganglionic storage process simultaneously involving neurons throughout the nervous system. Some limited morphologic evidence has been presented in the past indicating that function of the implicated ganglion cell is not significantly diminished until the disease process has appreciably advanced.[14,15] On the basis of rare case reports describing lipid storage within ganglion cells of stillborn infants, it might be surmised that the metabolic accumulation in the central nervous system lipidoses of infancy may commence in utero.

Still further evidence pointing to an onset of pathologic processes earlier than that suggested by clinical observation is available in biologic fluid enzyme level studies in afflicted infants.[7,8] Tests of this nature have shown marked elevations of serum and cerebrospinal fluid glutamic oxalacetic transaminase and lactic acid dehydrogenase levels in the early months of the disease with return toward the normal range as the disease progressed. Since the most profoundly abnormal values were obtained shortly after clinical recognition of IAFI, it was postulated that the levels of these enzymes might be even more strikingly abnormal in the paranatal period prior to the development of the classically recognized clinical symptoms. In two ostensibly normal infants (siblings of patients with IAFI) highly abnormal enzyme levels were obtained. In the succeeding few months the indisputable symptom complex of IAFI appeared.

Finally, it should be mentioned that careful anamnesis often points to a paranatal origin of the disease. Many mothers have stated that the first abnormality occurred during the fifth or sixth month of life, but casually added that their child had been unusually sensitive to loud noises since birth. Still other parents have attributed this hyperacusis to an unusual sensitivity of their child and only subsequently appreciated the grave significance of this symptom.

Therefore, while a conventional tabulation of the neurologic deficits of the disease has been made in the present study, it would appear more reliable to accept the hypothesis that the disease commences at or before birth and is only recognized when impairment of the functional integrity of the nervous system results in a recession from the lower limits of normal behavior as established by the parents.

Surprisingly few illnesses developed in the latent period before the onset of neurologic symptoms. Two of the IAFI infants had otitis media; one case of rubella and one of rubeola were also recorded. When infection was present, however, it was described as unusually severe. The parents of three of the children volunteered the information that healing of the circumcision was distinctly prolonged. A hypogammaglobulinemia has been noted in IAFI,[16] and such retarded healing may be its somatic reflection. It is also curious that no frank allergic manifestations were described by the parents at any time in the months prior to the determinate illness.

D. Duration of Illness

Duration of life after the appearance of IAFI symptoms varied more widely than did the time of onset of recognizable disease (Tables 6A, 6B). The shortest tenure was 4 months. At the other extreme, 17 infants survived longer than 36 months after the commencement of the illness. The average disease duration at the time of death was 24.1 months (average age at death, 29.5 months). No differences in duration of life were apparent between male and female patients. The time and clinical manner of onset of those children

who subsequently pursued a prolonged clinical course were in no way singular. Time of disease onset for IAFI children succumbing in Phase I was 6.1 months; in Phase II, 5.8 months; and in Phase III, 5.4 months. IAFI infants of non-Jewish extraction seemed to deteriorate more rapidly than Jewish infants with the same disease. Average age at the time of death in the former group was 26.0 months. Infants with NPD uniformly died at an earlier age than patients with IAFI (average age at death 19.1 months).

E. Familial Incidence

A complete medical history of all siblings of affected probands was required before acceptance of any kinship for study. The unequivocal character of IAFI made detection of the homozygous state no problem in review of the data. However, presumably normal infants below the age of 10 months were not considered, in order to exclude the possibility of a belated case of IAFI. Thus, in 102 examined kinships, a total of 122 infants with IAFI and 101 normal siblings were evaluated.

More than one child with IAFI was present in 20 of the 102 families analyzed. When the 23 families with only one child are subtracted from the 102 families in this series, the incidence of multiple cases of IAFI within the same family reaches 25%. The familial nature of the disorder is certainly beyond dispute. Sachs himself recognized the genetic component of the disease when a sibling of his first patient developed the same illness.[17] The hypothetical notions of environmental etiology expressed by many earlier observers at the turn of this century have since been effectively dissipated by quantitative evidence of a strictly recessive transmission. Certainly, there are no data to substantiate the claim that a ghetto existence, per se, potentiates and breeds the disease. If the illness were indeed more prevalent in such isolated subcommunities, it reflected more the concentration of heterozygotic carriers in such locations, abetted by the circumstances of measurably increased consanguinity.

It is assumed that a defined ratio of the progeny of two parents, each heterozygous for the disease, will show clinical evidence of the disorder (IAFI); statistical verification of a simple, recessive gene substitution disease, however, often requires large sibships. About 95% of the families in the present report were composed of three or fewer offspring (average 2.2 children per kinship). Many of the families were advised against further conception after one child had exhibited the disease. In an autosomal recessive disease with complete penetrance, one-fourth of all children will be theoretically affected and three-fourths will be subclinically heterozygous or free of any carrier potentiality. By the factorial expansion of the binomial $(X+3Y)^N$, where X represents disease homozygosity; Y, freedom from the deleterious gene, and N the number of children in the sibship, a practical proportion can be elaborated. Thus, for example, in families of two children the expression would result in an expansion of $X^2+6XY+9Y^2$. In 16 theoretical families, one sibship (X^2) would have both children afflicted, 6 sibships ($6XY$) would have one of the two children afflicted, and 9 sibships ($9Y^2$) would have neither visibly affected. In considering these 16 hypothetical two-children families, it is obvious that the 9 sibships without IAFI would go undetected and elude the statistical composite. Thus only 7 of the original 16 families would be available for evaluation. Therefore, of the 14 children derived from these 7 two-children families, 8 would be phenotypic of the disease (i. e., 57.1%). By a similar process, the expected rate of IAFI for families of three, four, and more children may be calculated.[18] Table 8 represents a comparison between the theoretically calculated and observed number of cases of IAFI in the sibships of varying size, comprising the present report. A very close concordance is apparent with inappreciable differences between predicted and

TABLE 8.—*Observed and Theoretically Calculated Number of Affected Children in 102 Infantile Amaurotic Family Idiocy Sibships*

A No. Children in Family	B * No. Families	C * Total No. Children (A×B)	D * No. Children with IAFI	E * % IAFI Observed	F † % IAFI Calculated	G % IAFI Observed (Slome Series [3])
1	23	23	23	100	100	100
2	48	96	59	61.5	57.1	61.9
3	25	75	31	41.3	43.2	53.8
4	3	12	4	33.3	36.5	28.6
5	2	10	3	30.0	32.8	40.0
6	0	0	0	—	30.4	25.9
7	1	7	2	28.6	28.8	21.4
	102	223	122		‡	

* Present series.

† Method of calculation described in text.

‡ Total theoretically calculated number of patients with IAFI in total sibships of 223 is 119.9 (Σ F×C/100) compared with observed number of 122 (Column D).

observed frequency. Slome's [3] data, separately incorporated into Table 8, also show agreement with calculated expectation.

Because of the clinical characteristics of IAFI, it is safe to presume that the detection probability of the disease (degree of ascertainment) approaches unity in the families under consideration. Under such circumstances it is possible to verify *directly* the total probability (p) of a child exhibiting the disorder. Applying Haldane's [19] equation for pooled data derived from sibships of varying size (eliminating one-child families), it is seen that p is 0.253 (Table 9). This probability is in accordance with the Mendelian proportion of a recessive disease with complete penetrance where p equals 0.25.

Wilson has stated that sporadic, rather than hereditary, traits are the usual manifestations of recessive diseases lethal before child-bearing age.[20] Rare examples of genealogically vertical disease manifestation in IAFI have been reported. The carefully documented R family [21,22] has demonstrated the existence of the disease in two consecutive generations. Goldfeder [23] has also described a family tree with the disorder

TABLE 9.—*Determination of Probability (p) of Infantile Amaurotic Family Idiocy Sibships with More than One Child*

Size of Sibship (s)	No. Affected in Sibship 1	2	3	No. Sibships (n_s)	No. Affected in Sibships of Size s (r_s)	Total No. Offspring (sn_s)
2	37	11	0	48	59	96
3	19	6	0	25	31	75
4	2	1	0	3	4	12
5	1	1	0	2	3	10
6	0	0	0	0	0	0
7	0	1	0	1	2	7
				79	99	200

s = size of sibships.
n_s = number sibships of size s.
r_s = number affected in sibships of size s.
sn_s = total number of offspring in families of size s.

$$p = \frac{\Sigma r_s}{\sum_s \frac{sn_s}{(1-q_s)}}$$

p = probability of homozygosity = 0.253
$q = (1-p)$ = 0.747

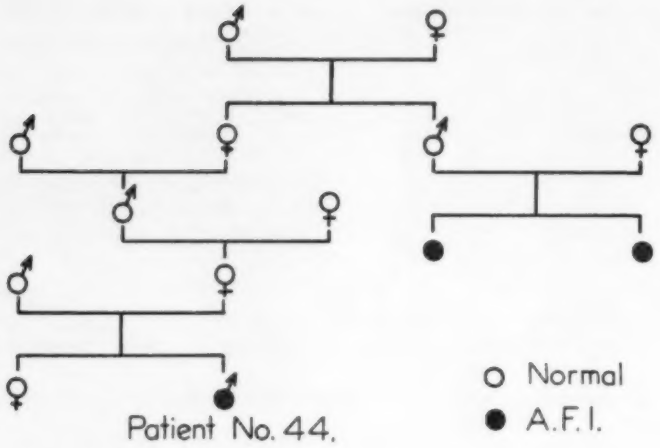

Figure 1

expressed in three succeeding generations. No parent-siblings (uncles or aunts of the afflicted patients) have evidenced IAFI in the present series. Very few of the normal siblings within the present kinships have reached the child-bearing age, so no comment can be made about the occurrence in the succeeding generation. In 6 of the 102 families (where adequate information was obtained) a more distant relative was affected by the disease. In Family 44, the maternal great-grandmother's brother fathered two children with IAFI (Fig. 1). In Family 52, the son of the maternal grandmother's sister was father of a child with unequivocal IAFI (Fig. 2). Case 101 is a second cousin of Case 73. A similar circumstance is seen in Case 131. A paternal second cousin died of IAFI (Case 111). Finally, a distant relative (maternal side) of Case 109 died of a disorder symptomatically suggestive of IAFI. The information concerning the occurrence of IAFI in more remote relatives was obtained with difficulty and only after careful exploration of the family arborizations. Most of such distantly related cases have been on the maternal side of the proband family.

No instance of central nervous system lipidoses were uncovered in the families of children with NPD or JAI.

F. Sex Incidence

IAFI is considered an autosomal recessive phenomenon with no apparent sex linkage. Earlier studies, however, stressed a slightly increased frequency in the female, and the data of Goldschmidt [6] and Slome [3] substantiate this. The case collations of Kozinn and associates [5] have noted a male

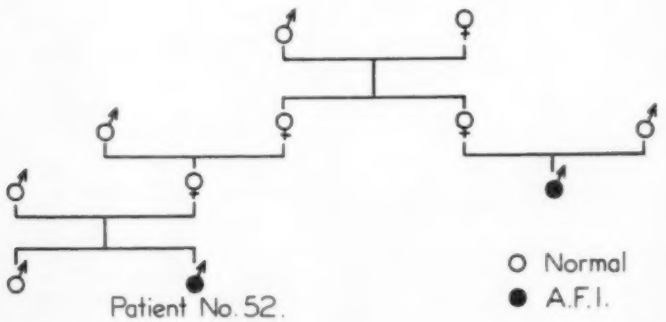

Figure 2

TABLE 10.—*Sibships in Niemann-Pick's Disease (NPD) and Juvenile-Amaurotic Idiocy (JAI)*

Diagnosis	Family No.	Order of Children 1	2	3	4	5
NPD	1, 2	♂ = ♂				
	40	♀				
	50	♂	♂			
	83, 83A	♀	♀			
	104, 105	♂	♂	♀		
JAI	102	♂	♀	♂	♀	
	126, 127	♀	♂	♀		
	132, 133	♀	♂	♂	♀	♂

♂ ♀ — affected.
♂ ♀ — unaffected.
= — twins.

predominance. A similar finding is evident in the present series. When the cumulative data of the four series are analyzed, only a negligible male preponderance is seen and probably in concordance with the excess of male births in the general newborn population (Table 10).

The increased number of females affected by IAFI in Slome's compilation is not indicative of any sex difference in incidence. Review of his statistics shows that 55.5% of all males and 55.7% of all females were afflicted with the disorder. Thus, the increased number of female patients reflects the majority of female offspring in the total sibship population. Similarly in the present series, where male IAFI patients predominate, the cumulative sibling population also shows a total excess of males.

The over-all uniformity in sex incidence may well conceal a possible distinction in this sex incidence relative to birth order. A further assessment of the present group discloses an as yet unexplained circumstance. Sufficient numbers of IAFI children, for statistical consideration, are available in the first three orders of birth. The frequency of disease of females in the first-born total female group is higher than in the second-born female group, which in turn is higher than in the succeeding female birth orders. In contrast, the percentage of affliction in male infants rises with succeeding rank of birth (Table 11). None of the other major genetic reviews of IAFI specify the order of birth by sex but some limited genealogical information is present in the appendix of Slome's survey. The sex of all sibship members is stated in 37 of his accumulated families. In 21 such families, the offspring were limited to one or two children. IAFI was described in 83% of all female children and 78% of all male children in this category. In Slome's sibships exceeding five children, the incidence of IAFI in females drops to 33% while in males it is noted in 63%. Thus it appears that the incidence of females with IAFI is relatively higher in the first birth order (or when the sibships are limited to one or two children), than in subsequent birth orders (or when the sibships exceed three children). The notable discrepancy in sex frequency seen in the various series described above may therefore also be a reflection of the numeric size of the individual fraternities.

TABLE 11.—*Relationship of Order of Birth upon Sex Frequency of IAFI in Affected Sibships*

	Order of Birth 1				2				3			
	Total No. Sibs.	No. with IAFI	% with IAFI	p *	Total No. Sibs.	No. with IAFI	% with IAFI	p *	Total No. Sibs.	No. with IAFI	% with IAFI	p *
Male	59	31	52.5	—	41	26	63.4	.16	17	12	70.6	.11
Female	43	23	53.5		38	18	47.4		14	6	42.9	
Total	102	54	52.9		79	44	55.7		31	18	58.1	

* p = probability of significance of difference in proportions.

Data concerning sex distribution in the cases of NPD and JAI may be found in Table 9.

G. Data on Geographic Places of Origin

While the Hebraic substrate of IAFI has been fully appreciated in many survey reports, further experience has shown that the abnormal gene is not homogeneously distributed throughout the Jewish population. Jews have been considered in three ethnic categories. The first of these designates the Ashkenazic communities within the geographic area of central and eastern Europe. The Sephardic Jews are traced to the western Mediterranean regions. The third of the groups represents those resident in the Middle East. Goldschmidt and associates have shown that the incidence of IAFI in the first group (derived from central and eastern Europe) is significantly higher than in the two succeeding groups.[6] The lowest incidence of IAFI was noted in the Oriental and African communities of Jews.

Of the 408 grandparental predecessors of the 102 Jewish kinships in the present survey, 78 were born in the United States. No attempt was made, in these instances, to determine place of birth beyond this generation. Ten further grandparents were born in Europe, but the precise location was unknown. The place of birth of 320 grandparents was used for compilation (Table 12). The majority took origin in northeastern Europe (Poland, Baltic States, and North Russia). A smaller fraction were born in central Europe and less than 8% were traced to western Europe (Germany, France, and England). A total of 93% of these grandparents born in Europe originated in northeast and central Europe.

While we have found no accurate statistics of the geographic heritage of American Jews, approximate estimates are available. It is believed that at least 20% of first-generation American Jews of present childbearing age are the progeny of west European parents, a fraction significantly higher than the percentage of IAFI families originating in that region. Of the 75 kinships where one or more grandparents on each side was born in Europe, 96% contained at least one maternal grandparent and one paternal grandparent emigrating from northeastern Europe. Only one kinship of the 102 studied was characterized by at least one grandparent (maternal and paternal) born in western Europe without the coex-

TABLE 12.—*Countries of Origin: Grandparents of Jewish Children with Infantile Amaurotic Family Idiocy*

	Maternal				Paternal				
	Grandmother		Grandfather		Grandmother		Grandfather		Total
Place of Origin	No.	% *	No.	% *	No.	% *	No.	% *	Percentage *
United States	21		17		16		8		
Northeast Europe		66.7		67.1		75.6		73.6	70.8
Russia	29		34		34		40		
Baltic States	5		3		6		5		
Poland	18		20		22		22		
Central Europe		28.2		27.0		18.3		18.7	22.9
Austria	10		10		3		5		
Hungary	4		5		0		0		
Czechoslovakia	5		4		6		6		
Rumania	3		4		6		6		
Western Europe		5.1		5.9		3.7		7.7	5.7
Germany	4		3		3		3		
England	0		2		0		2		
France	0		0		0		2		
Near East	0	0	0	0	2	2.4	0	0	0.6
Unknown	3		0		4		3		

* Percentage of foreign-born where country of origin is known.

TABLE 13.—*Countries of Origin: Grandparents of Non-Jewish Children with Infantile Amaurotic Family Idiocy*

Place of Origin	Maternal		Paternal	
	Grand-mother	Grand-father	Grand-mother	Grand-father
United States	3	2	2	2
Western Europe	0	1	1	1
Central Europe	1	1	0	0
Southern Europe (Italy, Spain)	0	0	1	1

TABLE 14.—*Countries of Origin: Grandparents of Children with Niemann-Pick's Disease and Juvenile Amaurotic Idiocy*

Place of Origin	Niemann-Pick's Disease			
	Maternal		Paternal	
	Grand-mother	Grand-father	Grand-mother	Grand-father
United States	1	1	1	3
Northeastern Europe	3	2	2	1
Central Europe	1	1	0	0
Asia Minor	0	1	0	0
	Juvenile Amaurotic Idiocy			
United States	3	3	2	1
Western Europe	0	0	1	2

istence of east European forebears. In contrast, none of the grandparents in the four non-Jewish IAFI families originated in northeastern Europe. Two of these grandparents were born in Yugoslavia, the rest in Italy, Scandinavia, Germany, and Central America (Table 13).

A heavy preponderance of northeastern and central European background is also apparent in the small number of NPD cases presently studied (Table 14). In contrast, none of the grandparents within the JAI family constellations derived from central or eastern Europe. Foreign births in this category were confined to northwestern Europe. This is in agreement with Sjögren's observations noting that almost all cases of this disorder were traceable to Scandinavia, Germany, and the British Isles, the majority of cases confined to isolated communities in Sweden.[24]

H. Religion

The religion of the grandparents has been documented in the 111 kinships. The predominantly Hebraic antecedence of IAFI is substantiated in the present series. All four grandparents were Jewish in 104 sibships and some Jewish forebears were identified in both maternal and paternal lineage of three further families. Of the four remaining families, no Jewish ancestry was recorded at the grandparent level. One of these latter families (Family 117-118), of Norwegian descent, did contain a maternal great-grandmother who was Jewish. Another of the non-Jewish patients represented the first morphologically substantiated example of IAFI in the Negro. The diagnosis was not entertained during life and was established only after histologic examination of the brain.

In Slome's[3] review of IAFI, a 14.2% incidence of gentile parentage is noted. The definition of Jewish genealogy, however, is not discussed. It is conceivable that an IAFI child of declared Christian religion may represent the concurrence of bilateral Jewish forebears two or more generations back and yet be classified as a non-Jewish example of IAFI. Ktenidès records an even higher percentage of gentile cases (39.8%) based upon her review of 104 families. The problem of what constitutes a designation of Jewish or non-Jewish background again appears. Further, since the chances of a non-Jewish case emerging in the literature is far greater, it is reasonable to assume that data based solely upon published cases would incorporate this disproportion. Kozinn and associates,[5] reviewing the death certificates of New York City, found 5% of their cases derived from non-Jewish parentage.

All of the seven cases of NPD in the present report were of Jewish origin. Crocker and Farber[25] described a 30% Jewish incidence in their cases of NPD, but stated that their patients were extracted from a more heterogeneous population.

None of the patients with JAI were Jewish. Jervis,[20] in reviewing the literature concerning this disease, has failed to find a single indisputable instance of the disorder existing in a Jewish family and has expressed the opinion that the close histologic similarities between the two forms of amaurotic idiocy do not indicate a common or overlapping genetic background.

I. Incidence of Consanguinity

The potentiating role of intermarriage is an important consideration in rare, recessive disorders. An inverse correspondence between the incidence of consanguinity and the infrequency of the carrier gene rate has been postulated (i. e., the rarer the recessive disease in any population, the higher the incidence of blood relationship in the carrier families). Slome[3] and Ktenidès[4] noted a 23.0% and 18.6% consanguinity incidence respectively in their Jewish cases of IAFI, and a 55.6% and 33.3% incidence in their non-Jewish cases. Goldschmidt and associates[27] estimated the rate of consanguinity in the Ashkenazic (northeastern European Jewish) population of Israel at about 1%, while in those families of such geographic origin bearing children with IAFI the rate was 10%. It is interesting to note that, although consanguinity is encountered more commonly in the Mediterranean and Near East Jewish communities,[27] the incidence of IAFI is significantly less than is found in the Jewish population traceable to northeastern Europe. This discrepancy has prompted Kozinn[5] to suggest that IAFI may have unilaterally originated in eastern Europe, involving Jewish fraternities of different ethnic backgrounds by slow spread.

No consanguinity of first order was evident in the presently studied kinships. In six families, however, more remote intermarriage was disclosed. In one case (Family 49) the paternal and maternal great-grandfathers were brothers. In three instances (Families 54, 70, and 89-90) first-cousin marriages were consummated by the maternal grandparents; in Family 20, in one of the maternal great-grandparent unions and in the paternal grandparent union, a first-cousin intermarriage was recorded. Husband and wife were second cousins in Family 95. In none of the non-Jewish families of IAFI was a history of consanguinity elicited. These figures certainly do not approach the high order of blood relationship marriages characteristic of the European monographs concerning IAFI. In Kozinn's[5] survey of cases within New York City, he found no instance of consanguinity either.

Another possible measure of remote, potential consanguinity is the determination of similarity in locales of origins of the grandparent unions. Such an approach is at best inferential. Of the paternal grandmother-grandfather marriage participants 73% were born in the same province, while 51% of the maternal grandparent marriage partners were traced to the same area of Europe.

J. Data Concerning Relatives of Children with IAFI

The gathered medical information concerning 1,793 relatives of 122 children with confirmed IAFI failed to indicate any illnesses which could be construed as abortive or incomplete variants of IAFI (other than the 6 cases referred to above). There was no indication of any unusual number of cases of mental deficiency, retinal disease, or motor disturbances in this population. The only instance of suggestive correlation was in Family 77, where the paternal grandfather suffered from bilateral primary macular degeneration of unknown etiology, commencing in middle-adult life and resulting in almost total blindness within a period of 10 years. Other than the amaurosis this man displays no abnormalities of a neurologic nature and continues to manage a large commercial enterprise.

1. *Siblings.*—Records of 101 siblings of the patients with IAFI were studied. No serious illnesses were encountered. All the children are presently alive and of average intelligence and physical development. No

neurologic disturbances of any type were found.

2. *Fathers.*—The vast majority were born in the United States. A review of childhood diseases disclosed no unusual preponderance of any illness. In only two instances was there any neurologic disorder noted (febrile convulsions of infancy and congenital nystagmus) and these of only vague import. Adolescence and young adult life was medically uneventful. No instances of mental retardation or visual disturbances developed in any of the fathers questioned. A large percentage were uneventfully accepted into the armed services within the previous 18 years. Occupations varied widely, the majority employed as independent business men. About 5% were practicing physicians or dentists. None of the fathers in the present series, other than those engaged in the medical profession, were in occupations characterized by exposure to ionizing radiation. No occupations with potential or actual exposure to toxic substances were recorded. Illnesses of the adult period were not prominent, and were generally of an infectious nature when present. No somatic anomalies were described. All the fathers are actively engaged in their respective vocations at present. As a group they represent a fundamentally healthy population of normal intellect.

3. *Mothers.*—Most were born in the United States. Childhood and adolescence were medically unremarkable except in Family 18, where the mother developed premature cataracts. The adult life of the 102 mothers under consideration showed no preponderance of any illnesses and complete absence of any neurologic disturbances. All the mothers are presently alive and healthy.

4. *Paternal Siblings.*—In the 102 families, there were 235 paternal siblings. Five of these died before the age of 21 from a range of dissimilar circumstances (bronchitis, omphalitis, cerebral hemorrhage of unknown cause, diphtheria, and Hodgkin's disease). The remaining siblings are presently alive. In the latter group, one brother presently has multiple sclerosis; one sister has diabetes mellitus, and one other sister, leukemia. No other sustained disorders were described. The great majority are married (86%) and have 322 children, all of whom are presently alive and presumably healthy. (One male child, at age 13, had a brief episode of febrile convulsions, but has recovered completely.) In the cumulative group of 567 paternal siblings and paternal-sibling offspring, only one case of organic neurologic origin (multiple sclerosis) was encountered. Based upon choice of occupation and extent of formal education, the adults comprising this group are of completely normal intelligence. No indication of mental retardation, visual disturbance, motor deficits, or any other fragment of the IAFI complex was uncovered.

5. *Maternal Siblings.*—Records of 205 maternal siblings were reviewed. Eight succumbed prior to the age of 21, of scarlet fever (one case), spina bifida (two cases, in same family), appendicitis (one case), infantile hydrocephalus (one case), pneumonia (one case), and prematurity (one case). One brother, mentally retarded since birth, died at the age of 24, and one further brother died of "cerebral thrombosis" at age 32. The remaining siblings are all presently alive. One living sibling was submitted to a unilateral nephrectomy because of a renal malformation but is presently healthy without further anomalous stigmata. One other living brother had mild diabetes. Of these siblings 88% have married (many of the unmarried are still in adolescence). These unions have produced 308 children, all of whom are presently alive. Illnesses in this category include one male child with leukemia, two children (siblings) with severe mental retardation, and one infant with celiac disease. The remaining sibling offspring are apparently healthy and free of any neurologic symptoms.

6. *Paternal Grandparents.*—Medical data concerning the paternal grandparents of the children with IAFI are brief, inadequate, and generally not subject to independent confirmation. Limited information on 164 grandparents, however, was obtained. No

unusual disease patterns were evident. Eight grandfathers died as the result of "cerebrovascular disease"; three paternal grandfathers had clinically obvious paralysis agitans; one paternal grandfather had epilepsy commencing late in life, and one grandfather died of an intracranial neoplasm, type undetermined. The survival rate and average age at death (excluding those perishing by traumatic agency) did not differ appreciably from the normal. No instance of dystonia musculorum deformans was uncovered in the survey. A specific search for this disorder (or the more fragmentary components of the syndrome such as spastic torticollis) was instituted because this dyskinetic disorder occurs predominantly in Jews of Russian extraction.

7. *Maternal Grandparents.*—The majority of the maternal grandparents are presently alive and healthy. One maternal grandmother succumbed to multiple sclerosis, and six maternal grandparents died as the result of intracranial vascular disease. No neurologic symptoms were uncovered otherwise.

8. *Paternal Relatives (Distant).*—Records of individuals in this category are distinctly incomplete and became available only when such information was volunteered. Two cases of multiple sclerosis were described in paternal second cousins, and individual instances of idiopathic epilepsy, paranatal brain injury, and deafness (otosclerosis) were recorded. Precocious cataract formation was present in two children of a distant relative in one family.

9. *Maternal Relatives (Distant).*—A distinctly greater number of neurologic diseases were described in the maternal relatives. The population base from which these cases were extracted, however, is unknown, and hence the relative frequency cannot be estimated. Two cases of multiple sclerosis (a maternal aunt and a maternal first cousin) were described. Seven relatives with epilepsy were also noted, three succumbing in childhood. Two maternal uncles died of infantile hydrocephalus, and a third cousin within still another family died of hydrocephalus. Two cases of presumed cerebral palsy were also noted in still another family. In addition to the recorded disturbances mentioned above, it was noted that a history of severe epilepsy on the maternal side of the family was recorded in all four non-Jewish IAFI kinships. In this latter category, a maternal aunt died of epilepsy at the age of 22 in the first family; a second cousin died of epilepsy at the age of 28 in the second family; a first cousin died of epilepsy with associated mental retardation at the age of 34, and a maternal uncle died of epilepsy at the age of 19 in the fourth family.

K. Data Concerning Relatives of Children with NPD and JAI

The parents of the children with NPD are all presently alive and healthy with no apparent medical disturbances. One sibling of one child with NPD, died in infancy of "pulmonary anomaly." One paternal grandfather had paralysis agitans.

The parents of the children with JAI are presently alive and healthy. None of the siblings of the five cases of this disturbance exhibit any serious illnesses. One paternal grandfather died of cerebrovascular disease. A maternal cousin died of a brain tumor, type unknown. A history of diabetes mellitus was elicited on the maternal side in each of the three families. In one family, an aunt and three cousins had diabetes. In the second family one aunt and, similarly, in the third family, one aunt suffered from this metabolic disorder. One of the children with JAI (Case 126) died at the age of 8 years in diabetic coma.

Summary

One hundred thirty-one confirmed cases of infantile amaurotic family idiocy were statistically evaluated in regard to nature of birth, time and manner of inaugurating abnormalities, duration, family background (illnesses, places of origin, religion, consanguinity), and familial and sex incidence.

In conformity with previous observations, the large majority of the patients were of Jewish extraction with antecedents derived

from northeastern Europe. The probability of homozygosity was calculated and shown to indicate a recessive disorder with complete penetrance.

Eight patients with Niemann-Pick's disease and five patients with juvenile amaurotic idiocy were similarly assessed.

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The Prophylaxis of Streptococcal Infections in Patients with Rheumatic Fever

A Comparison Between Sulfadiazine and Erythromycin

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The relationship between group A streptococcal infections and the subsequent occurrence of rheumatic fever has been well established. It has also been shown that initial and recurrent attacks of rheumatic fever can be prevented if streptococcal infections are prevented or effectively treated.[1] Several antibacterial agents have been employed for the prophylaxis of streptococcal infections in patients with rheumatic fever or rheumatic heart disease.[2] Sulfadiazine and penicillin are the two agents most widely used. Sulfadiazine prophylaxis has greatly reduced the incidence of streptococcal infections and recurrence of rheumatic fever, but protection is not complete and 5% to 10% of patients develop reactions to the drug.[2] Penicillin prophylaxis has proved to be more effective than sulfadiazine prophylaxis, but reactions also develop in 2% to 5% of persons receiving penicillin.[3] Because of the shortcomings of sulfadiazine and penicillin, it seemed desirable to investigate other antimicrobial drugs as prophylactic agents against streptococcal infections. Erythromycin, which has been shown to be effective against group A streptococci and to be relatively nontoxic, was chosen for this study.[4] The data presented compare the efficacy of erythromycin with sulfadiazine in the prevention of group A streptococcal infections and rheumatic recurrences in known rheumatic subjects.

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Description of the Study

Fifty children from the Vanderbilt Hospital Pediatric Cardiac Clinic in whom the diagnosis of rheumatic fever or rheumatic heart disease had been established were included in this study. A modification of the criteria established by Jones was used for the diagnosis of acute rheumatic fever.[5] The diagnosis of rheumatic heart disease was made by the presence of murmurs of mitral stenosis, mitral insufficiency, or aortic insufficiency. Twenty-five of the children were selected at random and placed on continuous sulfadiazine prophylaxis of 0.5 gm. morning and night. The remaining 25 were placed on erythromycin (Ilotycin, Lilly)* 100 mg. morning and night. Most of the patients in both groups who were seen in their acute attacks were admitted to the hospital for several weeks and subsequently sent to a convalescent home. All children were followed closely at two- to three-week intervals in the Cardiac Clinic during the active phase of their disease and at increasing intervals up to every three months after the signs of rheumatic fever had subsided. During each clinic visit throat cultures for β-hemolytic streptococci were obtained. In addition, an erythrocyte sedimentation rate (Wintrobe, uncorrected), hematocrit reading, leukocyte count, urinalysis, antistreptolysin O titer, and C-reactive protein titer were done. Electrocardiograms and cardiac fluoroscopy were performed as needed in accordance with the progress of the disease. β-Hemolytic streptococci were identified serologically according to the methods of Maxted[6] and Swift, Wilson, and Lancefield.[7] Antistreptolysin O titers on all sera from each patient were determined concomitantly, if possible, by a modification of the technique of Hodge and Swift.[8]

* Supplied by the Eli Lilly Company.

TABLE 1.—*Comparability of the Groups Receiving Sulfadiazine or Erythromycin Prophylaxis*

	Sulfadiazine (25 Patients)	Erythromycin (25 Patients)
Average age (years)	12.1	10.6
Sex { Male	9	19
Sex { Female	16	6
No. observed continuously since last attack of acute rheumatic fever	24	23
No. with inactive rheumatic fever at start of study	9	2
Average period of observation during study (months)	20	19.5
Total number of cultures obtained	305	369

Rises of two-dilution increments (0.2 log) were considered significant.

Patients who showed a positive culture for β-hemolytic streptococci were treated with penicillin as soon as possible, without waiting for the group classification of the isolate. Treatment consisted of the intramuscular administration of several forms of penicillin or oral phenoxymethyl penicillin (penicillin V) in regimens designed so that all patients would receive treatment for a minimal period of seven days.

Results

Comparability of the Groups Receiving Sulfadiazine or Erythromycin Prophylaxis.

To determine if the groups receiving sulfadiazine or erythromycin were comparable, several characteristics of the groups were considered and are presented in Table 1. The average age of the patients receiving sulfadiazine was 12.1 years, and of the patients receiving erythromycin 10.6 years. There were 9 males and 16 females in the sulfadiazine group, and 19 males and 6 females in the erythromycin group. Of the patients in the sulfadiazine group 24 had been followed regularly in the cardiac clinic since their most recent attack of acute rheumatic fever; of this group, 9 were thought to be in an inactive phase of the disease at the start of this study. Of the children in the erythromycin group 23 had been examined regularly since their most recent attack of rheumatic fever, and 2 were considered to be in an inactive phase at the time they were placed in the study. The patients receiving sulfadiazine prophylaxis were observed for an average period of 20 months, none less than 7 months; those on erythromycin prophylaxis were observed for an average period of 19.5 months, none less than 9 months. A total of 305 throat cultures were obtained from the patients receiving sulfadiazine and a total of 369 from those receiving erythromycin. Although there were differences between the two study groups, it was thought that the groups were similar enough to allow comparison of the effect of the two prophylactic programs.

The Occurrence of β-Hemolytic Streptococci in Throat Cultures.—The occurrence of β-hemolytic streptococci in the throat cultures of the patients receiving sulfadiazine or erythromycin prophylaxis is shown

TABLE 2.—*The Occurrence of Beta Hemolytic Streptococci in Throat Cultures of Rheumatic Fever Patients on Sulfadiazine or Erythromycin Prophylaxis, and the Association with Symptoms of Respiratory Infections, Antistreptolysin Responses and Rheumatic Recurrences*

		Patients with Positive Throat Cultures			
Prophylaxis	Classification of Streptococcus Isolated	Total Positive	No. with Symptoms of Respiratory Infection	No. with Significant ASO Rise	No. with Recurrence of Acute Rheumatic Fever
Erythromycin (25 patients)	Group A	1	1	0	0
	Non-Group A *	6	4	3	0
	Unclassified	1	0	1	0
Sulfadiazine (25 patients)	Group A	7	4	3	1
	Non-Group A *	4	1	2	0
	Unclassified	2 †	2	1	0

* The isolates from one patient in each prophylaxis group were classified as group G; the remaining culture could not be classified as A, B, C, D, or G.

† These 2 patients also had separate episodes during which group A streptococci were isolated.

in Table 2. β-Hemolytic streptococci were isolated at some time during the study from 11 of the 25 patients receiving sulfadiazine. Streptococcal isolates from seven of the patients were classified as group A streptococci and four as non-group-A. Two of the patients from whom group A streptococci were isolated also had, on one separate occasion each, streptococcal isolates which were not classified. β-Hemolytic streptococci were isolated from 8 of the 25 patients receiving erythromycin. The isolate from one of these patients was identified as a group A Streptococcus; six other isolates were found to be non-group-A streptococci, and one was not classified. In the erythromycin group, one of the non-group-A isolates was classified as a group G Streptococcus and the other 5 isolates could not be classified with group A, B, C, D, or G antisera. In the sulfadiazine group one of the non-group-A cultures was identified as a group G Streptococcus, and the other three could not be classified with the available grouping of sera (groups A, B, C, D, and G).

Because the success of any prophylactic program using oral medication depends on the cooperation of the patient, an effort was made to determine whether prophylaxis had been omitted prior to positive cultures of group A streptococci. One of the seven patients on sulfadiazine with a positive culture and the single patient on erythromycin with a positive culture admitted having taken prophylaxis irregularly.

These data suggest that erythromycin was more effective than sulfadiazine in preventing the occurrence of group A streptococci. While it would appear that a significantly larger number of patients in the sulfadiazine group than in the erythromycin group harbored group A streptococci, the numbers involved are small and of borderline significance. No difference was shown in the occurrence of non-group-A streptococci in the two prophylactic groups.

Table 2 also shows the association between positive cultures for β-hemolytic streptococci and the occurrence of symptoms of respiratory infection, antistreptolysin response, and recurrence of rheumatic fever. The one positive culture for group A streptococci in the erythromycin group was associated with clinical symptoms of a respiratory infection, but there was no significant rise in antistreptolysin titer and the patient did not develop a recurrence of rheumatic fever. Four of the seven patients on sulfadiazine, at the time of the positive cultures for group A streptococci, had clinical symptoms of respiratory infection, including fever and sore throat. Three of these seven had significant antistreptolysin O titer rises. The only recurrence of rheumatic fever occurred in this group and was in a patient who had shown no signs of rheumatic activity for four years. This recurrence was characteristic by the appearance of arthritis and carditis, and the child denied having omitted prophylaxis. This patient was one of three who showed a significant rise in antistreptolysin. There was a concomitant rise in the C-reactive protein level and the erythrocyte sedimentation rate.

One additional patient in the sulfadiazine group had a significant antistreptolysin rise that was not associated with a positive throat culture for streptococci. At this time this child also exhibited mild joint pains, weight loss, increased fatigability, a prolonged P-R interval on the electrocardiogram, and an erythrocyte sedimentation rate of 47. These findings were transient and difficult to interpret because they occurred when the patient was considered to be in the convalescent phase of a recent rheumatic attack. With the exception of this case none of the patients on either drug who failed to show positive cultures for β-hemolytic streptococci had a significant rise in antistreptolysin at any time during this study.

One of the patients receiving sulfadiazine, from whose pharynx group A streptococci had been isolated 20 months earlier, developed a skin infection from which

group A streptococci were cultured. This patient was treated locally with bacitracin ointment, and there was no associated antistreptolysin titer rise or finding suggestive of a rheumatic recurrence.

With the exceptions mentioned above, none of the other patients in either group from whom group A streptococci were isolated showed significant changes in C-reactive protein levels or erythrocyte sedimentation rates subsequent to the positive cultures.

One of the four patients on sulfadiazine with a culture for non-group-A streptococci showed clinical symptoms of a respiratory infection. Two of these patients had a significant rise in antistreptolysin, but there were no rheumatic recurrences. Of the six patients on erythromycin who had positive cultures for non-group-A streptococci, four had clinical symptoms of respiratory infection and three had significant rises in antistreptolysin. None showed rheumatic recurrences. None of the positive cultures for non-group-A streptococci in either group was followed by significant changes in either C-reactive protein level or erythrocyte sedimentation rate.

Occurrence of Untoward Reactions to Sulfadiazine or Erythromycin.—There were no untoward reactions to either drug, as evidenced by a reduction in the leukocyte count, an abnormal urinalysis, or unusual clinical symptoms or signs.

Comment

Sulfadiazine has been used for a number of years as a chemoprophylactic agent against group A streptococcal infections in patients who have had rheumatic fever. Although it is recognized that sulfadiazine will not eradicate streptococci from the pharynx in acute streptococcal infections,[9] it has been shown [2] that continuous administration of this agent in small doses (0.5-1.0 gm.) will reduce the incidence of streptococcal infections and rheumatic fever about 85%. It has the advantage of being inexpensive, which must be taken into account when one considers years of medication; it is palatable, and it does not have to be given on an empty stomach. The chief disadvantages of sulfadiazine are that it does not eradicate the Streptococcus from the pharynx; it must be given daily; it is not completely effective, and 5% to 10% of patients develop toxic or allergic reactions. During World War II the development of sulfonamide-resistant strains of streptococci made the use of sulfadiazine impractical for use in military populations. Sulfonamide-resistant strains, however, have not proved to be a problem in rheumatic populations.

Penicillin has also been used for several years as a prophylactic agent in rheumatic patients, and will prevent most streptococcal infections when given in daily doses orally or in monthly injections as benzathine penicillin G.[1,10,11] Penicillin has the advantage of being able to eradicate the group A Streptococcus from the pharynx if given in sufficient doses over a long enough period of time. Penicillin is more expensive than sulfadiazine, and if given orally must be given on an empty stomach to be maximally effective. As with sulfadiazine, oral penicillin must be remembered daily to be effective, and intramuscular benzathine penicillin injections are frequently painful and require monthly clinic or office visits. In the past, reactions to penicillin have not been as frequent as reactions to sulfadiazine, but an increasing number of serious reactions are being reported,[12] and studies have indicated that 2% to 5% of adults show some type of reaction following the injection of benzathine penicillin.[3]

Because neither sulfadiazine nor penicillin, which are the chief drugs used in the prevention of streptococcal infections, have proved to be ideal agents, this study was designed to test the efficacy of another agent, erythromycin. Erythromycin was chosen because it has been shown to be effective in vitro [13] and in vivo [4] against the group A Streptococcus and because few reactions to this drug have been reported.

At the present time this agent is more expensive than sulfadiazine or penicillin and must be given daily to be effective, but it was thought that these disadvantages were overweighed by the need for another effective prophylactic agent against group A streptococci. While the number of patients observed in this study was small, erythromycin was probably more effective than sulfadiazine, and only one patient receiving erythromycin acquired a group A Streptococcus. This is in contrast to the acquisition of group A streptococci by seven patients receiving sulfadiazine. In addition, none of the 25 patients receiving erythromycin for from 9 to 24 months developed any type of reaction to the drug. It would appear, therefore, that erythromycin is a safe and effective agent for the prophylaxis of streptococcal infections. This conclusion is in accord with that of Healey and Simon, who reported on their experience with erythromycin for short periods of time in 122 rheumatic children 6 to 16 years of age.[14]

Only one child in this study developed a recurrence of rheumatic fever. This patient was in the sulfadiazine group, and when seen with an acute throat infection, which was accompanied by a positive throat culture and antistreptolysin rise, already had a swollen joint. It is not known if recurrences in other patients were prevented by prompt treatment of their streptococcal infections with penicillin, but this seems a possibility since a high percentage of rheumatic patients develop recurrence following untreated streptococcal infections.[15]

The isolation of non-group-A streptococci from these patients is of interest. Rheumatic fever has not been associated with hemolytic streptococci other than group A, so the occurrence of these organisms in the patients receiving prophylaxis is of no significance as far as recurrences of rheumatic disease is concerned. On the other hand, since non-group-A streptococci can rarely be differentiated from group A streptococci by cultural characteristics, and because there is usually a delay of several days in the group classification of streptococci, it is necessary to institute therapy without delay in order to be certain that all group A streptococci are eradicated. It should be emphasized, however, that the group classification of hemolytic streptococci is highly desirable. Some non-group-A organisms are resistant to penicillin,[16] and treatment with this agent cannot be expected to eradicate them from the throats of patients. In contrast, while it is at times extremely difficult to eradicate group A streptococci, strains which are significantly resistant to penicillin have not been described,[17] and repeated or prolonged treatment with penicillin is usually effective.

The status of non-group-A streptococci as a cause of upper respiratory infections is not clear. Infections with these organisms in man are not thought to be common and non-group-A streptococci are usually associated with various diseases in animals.[18] The association in some of the cases described of the isolation of non-group-A strains with the occurrence of the clinical symptoms of respiratory infection and a significant antistreptolysin response suggests that these organisms might have been causative agents in these instances.

The antistreptolysin responses of the patients in this study are worthy of mention. It has been emphasized that patients who develop rheumatic fever following streptococcal infections show unusually high rises in antistreptolysin O titers.[19] It has also been shown that prompt eradication of streptococci from the throats of patients will result in a reduced or absent antistreptolysin response.[20] The development of significant antistreptolysin rises in only three of the eight patients from whom group A streptococci were isolated was probably due to the prompt and vigorous use of penicillin in these patients.

Summary and Conclusion

Fifty patients with acute rheumatic fever or rheumatic heart disease were followed for an average of 19½ months on two

chemoprophylactic regimens: 25 on sulfadiazine, 0.5 gm. twice a day, and 25 on erythromycin, 100 mg. twice a day. During this study there were seven patients with positive cultures for group A streptococci in the sulfadiazine group and only one such patient in the erythromycin group. One patient in the sulfadiazine group developed a recurrence of rheumatic fever. There were no untoward reactions to either drug. Erythromycin appeared to be superior to sulfadiazine in this study, and it is suggested that erythromycin may be a satisfactory long-term prophylactic agent against group A streptococcal infections in patients who have had rheumatic fever.

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Congenital Atrioventricular Dissociation Due to Complete or Advanced Atrioventricular Heart Block

Clinical and Cardiac Catheterization Findings in Twelve Children Without Cardiac Malformations, Including Three Siblings

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"Congenital heart block seldom occurs as an isolated abnormality. Many types of cardiac malformations have been reported with it. Septal defects, either auricular or of the high ventricular type, are by far the commonest of the malformations associated with this conduction disturbance." [1] These comments, published a decade ago, represented the opinion prevailing up to the past several years. Several authors [2-5] have now reported the frequent occurrence of congenital complete atrioventricular block in persons in whom no associated malformations can be demonstrated.

In complete atrioventricular heart block there is blockage of all atrial impulses, even when the ventricular rate is very slow, owing to extreme prolongation of the absolute refractory phase of the atrioventricular junctional tissue.[6] In complete atrioventricular dissociation with advanced atrioventricular block, the prolongation of the refractory phase is less, though marked, but the ventricular rate, though slow, is too rapid to allow the penetration of atrial impulses. Electrocardiograms of this type will resemble complete atrioventricular block. In incomplete atrioventricular dissociation with advanced atrioventricular block, the idioventricular rhythm is interrupted by an occasional conducted beat (ventricular capture). This type of rhythm is probably misinterpreted as complete atrioventricular block on most occasions, particularly if only short electrocardiographic tracings are taken. Incomplete atrioventricular dissociation of this type occasionally alternates with

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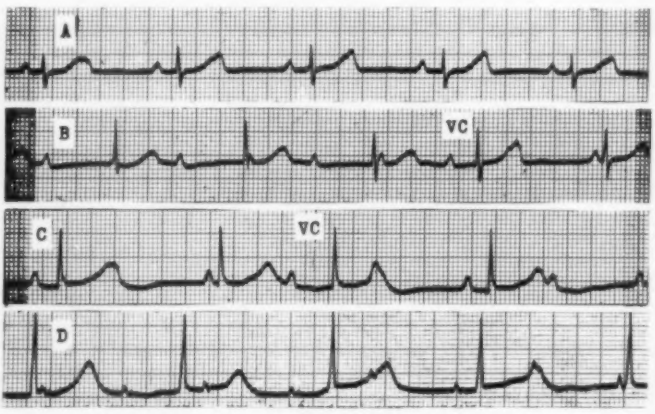

Representative electrocardiograms. Lead 2 in all. *A* (Case 11), Sept. 19, 1957, 2:1 atrioventricular block. Note that in this and following tracings, the P-P intervals enclosing QRS complexes are of shorter duration (ventriculophasic effect). *B* (Case 11), Nov. 4, 1957, atrioventricular dissociation due to advanced atrioventricular block. Note ventricular capture (VC) by atrial impulse. *C* (Case 8), atrioventricular dissociation due to advanced atrioventricular block. Note ventricular capture (VC). *D* (Case 7, sibling of Case 8), atrioventricular dissociation due to apparent complete atrioventricular block.

the more familiar 2:1 heart block. In all of these rhythm abnormalities, the atrial cycles (P-P interval) enclosing ventricular complexes will usually be shorter than the others (ventriculophasic effect). Examples of these phenomena are shown in the Figure.

Case Material

During the past eight years we have studied 28 children with bradycardia (ventricular rate 65 or below) due to atrioventricular dissociation secondary to either complete or advanced atrioventricular heart block, all presumably congenital. These cases are listed in Table 1 according to the type of block and the presence or absence of an associated cardiac malformation. It will be noted that cases of apparent complete block outnumber those with advanced block by about two to one. Associated congenital heart defects occurred in approximately half of the patients in each group. The sex distribution appeared random. The only heart defect to be frequently encountered in this series of cases was corrected transposition of the great vessels. We have previously emphasized the common occurrence of atrioventricular block in patients with this malformation.[7]

TABLE 1.—*Cases of Bradycardia Due to Atrioventricular Dissociation*

1. Atrioventricular dissociation with apparent complete atrioventricular block (18)	
*A. With no associated defects	7 (5 female)
B. With no apparent defects, but incompletely studied	1 (female)
C. With associated defects	10 (4 female)
(*a*) Atrial defect (one with partial anomalous pulmonary venous return)	2
(*b*) Ventricular septal defect	1
(*c*) Corrected transposition with patent ductus arteriosus and reversal of flow	1
(*d*) Corrected transposition with aortic valve defect	1
(*e*) Patent ductus arteriosus	1
(*f*) Tetralogy of Fallot (probable)	1
(*g*) Incompletely diagnosed, acyanotic	2
(*h*) Incompletely diagnosed, cyanotic	1
2. Atrioventricular dissociation with advanced atrioventricular block (10)	
*A. With no associated defects	5 (3 female)
B. With associated defects	5 (3 female)
(*a*) Ventricular defect with probable corrected transposition	2
(*b*) Single ventricle with pulmonary stenosis	1
(*c*) Situs inversus with levocardia, absent inferior vena cava, probable single ventricle with pulmonary stenosis	
(*d*) Incompletely diagnosed, cyanotic	1

* These 12 cases are the basis of the present study.

Only those 12 cases without an associated cardiac malformation are included in this study. In none was there a history suggesting syphilis, diphtheria, rheumatic fever, myocarditis, or digitalis intoxication. The clinical data are presented in Tables 2 and 3. Right heart catheterization was performed in all cases, and the results are shown in Table 4. General anesthesia was not used in these studies. The cardiac output was determined by the direct Fick principle.

Report of Familial Cases

CASE 7.—This 10-year-old girl was first seen at University Hospital in August, 1957. Fetal bradycardia had been noted in the eighth month of pregnancy, but this occasioned no difficulty, and delivery was normal. Bradycardia and a cardiac murmur were noted at birth. An electrocardiogram taken at 9 months of age showed complete atrioventricular dissociation, interpreted as complete atrioventricular block. The subsequent clinical course has been without incident, except for the occurrence of three episodes of fainting, one of which was interpreted as a Stokes-Adams attack by the attending physician. Repeated electrocardiograms over the years all showed complete atrioventricular dissociation presumably due to complete atrioventricular block (Figure). However, during cardiac catheterization at University Hospital in February, 1958, the continuous electrocardiograph tracing revealed areas simulating 2:1 atrioventricular block, during which times the ventricular rate tended to be slightly faster than during other periods. For 10 to 20 beats there would be a fixed P-R interval, though this interval varied in the different episodes from 0.08 to 0.32 seconds. This phenomenon of "synchronization" has been well described by others.[8]

CASE 8.—This 9-year-old girl, a sibling of Case 7, was also seen at University Hospital in August, 1957. A heart murmur had been noted at birth, but the heart rate was considered normal. At 6 years of age she had an electrocardiogram, and this showed atrioventricular dissociation with advanced atrioventricular block, the ventricular rate being 60 per minute. Subsequent electrocardiograms have shown similar findings (Figure). This patient has had no cardiac symptoms.

One younger sibling was reported to have died at the age of 6 days of congenital heart disease. On further investigation, it was learned that this infant had been the subject of a case report by Plant and Steven[9] in 1945. Bradycardia (60 per minute) had been noted for five weeks prior to birth, and a fetal electrocardiogram had verified this. Similarly, an electrocardiogram taken directly after birth also

TABLE 2.—*Clinical and Roentgenographic Findings*

	Case	Age: Present	Age: Bradycardia Noted	Age: First EKG	Symptoms	Murmurs	Blood Pressure Right Arm	Roentgenograms
Cases with apparent complete A-V block	1	2 yr.	2 wk.	2 wk.	Cyanotic spell at 4 days, with cardiac failure; now normal	Grade 2 sys. at apex; variable dias. at apex	90/—	Size 2+; vasculature normal
	2	10 yr.	5 yr.	7 yr.	Episode of pallor and nausea at age 5 yr.	Grade 2 sys. at apex	112/78	Size 2+; vasculature normal
	3	9½ yr.	At birth	5 yr.	None	Grade 3 sys. along LSB; variable dias. along LSB	98/50	Size 1+; vasculature normal; main PA 2+
	4	11 yr.	1 yr.	2 yr.	Poor growth	Grade 2 sys. along LSB; variable dias. along LSB	130/70	Size 1+; vasculature upper normal; main PA 2+
	5	7 yr.	Before birth	3 days	"Heart hurt" in earlier years	Grade 2 sys. along LSB	90/65	Size 1+; vasculature normal; main PA 1+
	6	8 yr.	3 yr.	3 yr.	None	Grade 3 sys. along LSB	115/60	Size normal; vasculature normal
	7	10 yr.	Before birth	9 mo.	Three episodes of syncope	Grade 2 sys. at apex., grade 2 dias. at apex and aortic area	146/76	Size 2+; vasculature normal
Cases with advanced A-V block	8	9 yr.	6 yr.	7 yr.	None	Grade 2 sys. along LSB	122/58	Size normal; vasculature normal
	9	3 yr.	7 mo.	2 yr.	None	Grade 2 sys. along LSB	115/50	Size 1+; vasculature normal
	10	12 yr.	5 yr.	7 yr.	None	Grade 2 sys. along LSB; variable dias. at apex	116/60	Size 1+; vasculature normal; main PA 1+
	11	3½ yr.	6 mo.	2 yr.	None	Grade 2 sys. along LSB; grade 2 dias. at apex	105/50	Size 1+; vasculature normal
	12	5 yr.	5 mo.	5 mo.	None	Grade 2 sys. along LSB	110/70	Size 1+; vasculature normal

TABLE 3.—*Electrocardiographic Data*

	Case	Age, Yr.	Rate A	Rate V	Axis	P Voltage and (Lead)	Longest QRS in Leads 1, 2, or 3	V1 Voltages R	V1 Voltages S	V1 Voltages R′	V6 Voltages q	V6 Voltages R	V6 Voltages S	T Wave
Apparent complete block	1	2	90	50	+120	2(2)	0.07	9	18	—	8	12	8	$+V_{R}V_{6}$
	2	7	110	50	+20	2.5(2)	0.06	2	9	5	2	26	1	$+V_{R}V_{6}$
	3	8	80	70	+60	2(2)	0.07	1	14	—	—	15	—	$+V_{R}V_{6}$
	4	11	80	50	+85	2.5(2)	0.06	2	5	—	3	30	—	$+V_{R}V_{6}$
	5	7	70	55	+75	3.5(2)	0.06	3	11	—	5	30	—	$+V_{6}$
	6	8	95	45	+70	2(2)	0.07	5	10	—	4	25	1	$+V_{R}V_{6}$
	7	10	100	45	+70	2.5(2)	0.07	—	19	—	—	28	—	$+V_{L}V_{6}$
Advanced block	8	8	85	50	+85	2.5(2)	0.06	5	30	—	1	7	1	$+V_{R}V_{6}$
	9	2	90	60	+90	2(1)	0.07	3	8	—	1	5	1	$+V_{R}V_{6}$
	10	8	80	56	+75	2(2)	0.08	2	7	—	1	25	2	$+V_{R}V_{6}$
	11	3	110	50	+80	2(2)	0.07	9	21	—	2	11	1	$+V_{R}V_{6}$
	12	5	120	57	+85	2.5(2)	0.08	8	32	—	1	23	—	$+V_{R}V_{6}$

showed a bradycardia due to complete atrioventricular dissociation (ventricular rate of 50 and atrial rate of 114). A systolic murmur was heard along the upper left sternal border. Roentgenograms showed considerable cardiomegaly. These latter two findings were attributed to the bradycardia. At autopsy, the heart was greatly enlarged (weighed 56 gm.). There were no gross malformations present, but the pulmonary conus was large. Special fixing and staining were done, but no Purkinje fibers could be identified in the ventricular septum. From the study of sections it appeared that there was either absence or imperfect development of the bundle of His. Death was attributed to a combination of cardiac failure, partial atelectasis of the lungs with early bronchial pneumonia, and birth trauma.

There were no other full siblings. The mother of these children died of disseminated lupus erythematosus in 1954. The father has since remarried and has a normal son by his second wife.

Clinical Findings

The clinical findings in isolated congenital atrioventricular dissociation due to complete or advanced atrioventricular block are usually minor, but may be unusual enough to raise the question of an associated malformation. A slow heart rate may be noted before birth, and it is only in such cases that one can strictly label the arrhythmia as congenital. Episodes of cyanosis, syncope, or pallor were noted in several of our patients. Patient 1 had cyanosis during the first three weeks of life, showed hepatomegaly and peripheral edema (interpreted at the time as cardiac failure), and did not begin gaining weight until 6 weeks of age. Symptomatology thus may be varied and at times severe. Neither Keith et al.[4] nor Paul et al.[5] encountered definite Adams-Stokes attacks in their 25 cases with atrioventricular block, though this has been described by others in cases of congenital [10] and acquired transient block.[11]

Easy fatigability is also described, but this complaint is always difficult to evaluate.

Cardiac murmurs are consistent findings in these children. As indicated in Table 2, there was typically a Grade 2-3 systolic murmur along the lower left sternal border or at the apex. Variable diastolic murmurs were noted frequently, in addition to the sounds of atrial contraction classically heard during ventricular diastole in cases of complete atrioventricular block. Similar findings have been described by Keith et al.[4] and Paul et al.[5] The latter have described the systolic murmur as early in time and of high frequency, and have attributed it to increased turbulence in the blood stream at the time of rapid increase in the rate of blood flow. Likewise, they have attributed the diastolic murmur to high blood flow velocity across the atrioventricular valves in early diastole. The first heart sound showed variability in intensity, the sound being loudest when atrial systole occurred shortly before ventricular systole. As would be expected with a bradycardia, there was usually a rather wide systemic pulse pressure.

Roentgen studies in our patients generally showed mild but definite cardiac enlarge-

TABLE 4.—*Cardiac Catheterization Data*

	Case	Age, Yr.	Surface Area, Sq. M.	Average Ventricular Rate per Min.	Oxygen Content, Vol/100 Ml. (Van Slyke Analysis)					Pressure, Mm. Hg and (Mean)			Systemic Index L/Min/ Sq. M.	Stroke Volume Ml/Sq. M.
					SVC	IVC	RA	RV	PA	BA or FA (Satur.)	RA	RV	PA	
Apparent complete block	1	11/12	0.38	60	11.0	10.0	10.9	10.1	11.2	17.2(99%)	15/3	50/0/2	50/15(M25)	2.55	43
	2	7	0.92	45	12.8	11.9	12.6	11.8	11.6	18.7(100%)		40/0/4	34/12(M18)	2.94*	65
	3	8	0.81	50	12.2	12.7	13.2	13.5	13.6	17.6(99%)	12/4	30/0/2	30/8(M20)	3.32*	70
	4	7	0.69	60	11.1	--	12.6	12.7	12.5	17.1(99%)	7/3	28/0/1	28/8(M12)	2.84	47
	5	7	0.90	59	11.5	11.4	12.1	11.7	11.5	16.3(100%)	8/4	33/0/6	28/10(M18)	3.59	61
	6	8	0.94	52	11.1	12.1	--	11.3	11.0	17.0(102%)	10/7	37/0/2	30/10(M16)	3.18	61
	7	10	1.39	50	12.8	12.9	13.0	13.1	13.2	19.6(99%)	12/5	30/0/6	30/10(M17)	2.54	51
Advanced block	8	9	1.16	46	14.2	--	14.6	14.4	14.3	20.0(100%)	6/2	34/0/6	28/11(M20)	2.46*	53
	9	2	0.49	60	8.3	11.8	10.8	9.3	9.7	16.7(97%)	12/5	45/0/4	42/18(M22)	2.64	44
	10	5	0.91	60	11.5	--	11.3	11.1	11.4	------	6/0	17/0/0	17/6	--	--
	11	2	0.56	60	10.8	10.2	11.5	11.3	10.9	15.2(96%)	7/3	30/0/1	20/8(M12)	2.62	60
	12	3	0.65	64	10.2	8.8	10.4	10.7	9.9	15.9(93%)	4/—2	34/4/0	22/4(M10)	2.66	42

* Based on actual oxygen consumption. In other cases, value of 172 ml. oxygen/min/sq. m. assumed.

ment, but the pulmonary vasculature was always within normal limits. The cardiac contour was normal in almost all cases, aside from the frequent occurrence of a prominent main pulmonary artery segment. These findings are in accord with the reports of others.[4,5]

Our patients all showed a supraventricular type of ventricular QRS complex on the electrocardiogram. Under such circumstances, it can be assumed that the pacemaker is high in the bundle of His or in the atrioventricular node. One can then favorably compare the tracings with those of normal children. In our cases the QRS electrical axis was within normal limits, the P waves tended to be upper normal in height, and the QRS duration tended to be upper normal. In some cases the precordial leads were suggestive of left ventricular hypertrophy, similar to the observations of Keith et al.[4] and Paul et al.[5] Where atrioventricular dissociation was interrupted by a ventricular capture, the P-R interval was strikingly prolonged, in the range of 0.22 to 0.40 seconds, but of consistent duration in the individual case. Similarly, where there was an intervening episode of 2:1 atrioventricular block, the P-R interval was again noted to be prolonged for the conducted beats. The ventriculophasic effect (Figure) was noted in all 12 patients, as well as in 12 of the 16 cases with associated cardiac malformations. These latter 16 cases also showed a supraventricular type of QRS complex, with several showing an incomplete form of right bundle branch block. Paul et al.[5] believe the presence of the latter feature is indicative of an associated septal defect.

Right heart catheterization revealed elevation of right ventricular and pulmonary artery pressures in several cases, with occasionally a mild differential in pressure across the pulmonic valve. Others have described similar findings.[5] The pressure differential across the pulmonic valve is not considered to represent an anatomical stenosis. Giant "A" waves were seen on the atrial pressure tracing whenever atrial sys-

tole coincided with ventricular systole. The calculated systemic blood flows (Table 4) proved to be considerably lower than we have generally found in normal children without heart block. The average of 2.96 L/min/sq. m. is considerably lower than the average of 4.55 in the cases reported by Paul et al.[5] Similarly, the arteriovenous oxygen difference in our cases averaged 5.9 ml. O_2/100 ml., as compared with a value of 4.0 in the latter study. None of our cases had general anesthesia. In three of our cases (Cases 2, 3, and 8) oxygen consumptions were done immediately after the catheterization, while in the others a value of 172 ml. O_2/min/sq. m. was assumed (the two groups showing similar values). The calculated stroke volume in our cases is thus in the normal range (54 ml/sq. m.), and considerably lower than the average value of 83 ml/sq. m. in the report of Paul et al.[5] who found this increase in stroke volume to be the most consistent hemodynamic abnormality. In order to bring our calculated flows and stroke volume into the range reported in the latter study, we would have to assume oxygen consumption in our cases to be 50% greater than measured or estimated (assuming increased oxygen consumption due to apprehension, e. g.).

Increases in cardiac output with exertion have to be achieved by increased stroke output, since the heart rate itself remains relatively constant at all times in children with complete block. If this mechanism is limited, then compensation for increased oxygen needs may be partially achieved by the removal of more oxygen per unit volume of blood (wider arteriovenous oxygen difference).

We have performed cardiac catheterization on a youngster who developed apparent complete atrioventricular block following closure of a ventricular septal defect. At the time of catheterization one year later, his rhythm had changed to a 2:1 block, with a ventricular rate of 43. Cardiac output, using an assumed oxygen consumption of 172 ml/min/sq. m., was 3.04 L/min/sq. m., with a stroke output of 70 ml/sq. m. Acquired block with bradycardia thus appears to present a picture quite similar to congenital block.

The total pulmonary resistance was found to be elevated in the majority of cases, but these values again are dependent upon the estimated or measured oxygen consumptions. This elevation may be due in part to possible increased left atrial pressure. In view of the relatively unsteady physiological state existing during and following cardiac catheterization, it appears unwise to draw definite conclusions from the limited physiological data we have obtained. Inasmuch as many of the clinical findings in children with complete block are attributed to an assumed increase in stroke output, further physiolgical studies under varying degrees of patient activity would be of value, in order to clarify the mechanisms by which these individuals adjust to increased oxygen demands.

Familial Aspects

Aylward[12] described two siblings with complete atrioventricular block, but mentioned no associated malformations. This report lacked electrocardiographic documentation, but Aitken[13] later indicated that this evidence had become available in these cases.

In 1947, Wendkos[14] reported two siblings with congenital complete atrioventricular block whose father had the Wolff-Parkinson-White syndrome with recurrent attacks of paroxysmal tachycardia. Although the older sibling had no clinical evidence of heart disease apart from the conduction defect, the younger sibling was found at autopsy to have a constriction in the distal portion of the aortic arch proximal to the entrance of a patent ductus arteriosus. A third sibling was normal. Familial cases of atrioventricular block have been reported also by Carp,[15] though the affected persons were over 60 years of age.

Our observation of atrioventricular block in three siblings is very striking, and suggests the possibility of a hereditary factor, at least in this family. Inasmuch as atrio-

ventricular block is one of the electrocardiographic findings that may occur in familial cardiomegaly,[16] it is possible that this family represents such an entity. Although none of our other cases gave a history of affected relatives, it would be of considerable interest and value to obtain electrocardiograms of the relatives of such cases, to see if there are lesser degrees of atrioventricular block present.

General Remarks

In the usual concept of atrioventricular dissociation, the ventricular pacemaker discharges more rapidly than the atrial pacemaker, and there is no retrograde activation of the atria. However, as pointed out earlier, atrioventricular dissociation may occur in the presence of advanced block, and in such cases the ventricular rate will be slower than the atrial rate. If the dissociation is nearly complete, with only occasional ventricular captures, then one can expect the clinical and physiological findings to be quite similar to those with complete atrioventricular block. It was for this reason that we included both groups in our study, limiting cases to those with bradycardia of 65 beats per minute or slower. As already noted, clinical and cardiac catheterization findings proved to be essentially the same in the two groups, except that cardiac symptoms occurred only among those with apparent complete block.

In reviewing our case material, we found that electrocardiographic tracings showing atrioventricular dissociation with advanced atrioventricular block had been generally interpreted as complete atrioventricular block. We believe that such confusion may be commoner than generally realized, particularly since atrioventricular dissociation with advanced atrioventricular block is not generally dealt with in the pediatric literature. Internists have been more aware of these complex conduction problems.[8,17] There may be a close relationship between congenital cases of apparent complete atrioventricular block and those with atrioventricular dissociation with advanced atrioventricular block. It is significant that almost all reported cases of "congenital complete atrioventricular block" are of the supraventricular type (normal QRS duration). In contrast, the QRS complexes tend to be wide in acquired block.[18] During right heart catheterization of patients with normal rhythm we have observed the development of apparent complete atrioventricular block, atrioventricular dissociation, or first or second degree atrioventricular block, sometimes interchangeably in the same patient. The presence of variable types of atrioventricular block and dissociation in siblings further suggests a common basis.

Perhaps the majority of congenital cases of apparent complete atrioventricular block are actually atrioventricular dissociation with advanced atrioventricular block, the ventricular rate being too rapid to allow penetration by the atrial impulse. The very favorable outlook for patients with congenital block contrasts sharply with that of patients who develop persistent complete block following intracardiac surgery. It has been our experience that the latter are subject to apparent Adams-Stokes attacks, with sudden death a common feature. If congenital block involves atrioventricular dissociation with advanced atrioventricular block, then one might expect ventricular capture to occur whenever the lower pacemaker becomes unduly slow, thereby preventing Adams-Stokes attacks. This aspect of congenital atrioventricular conduction disorders merits further investigation.

Summary

Clinical and cardiac catheterization studies were carried out on 12 patients with bradycardia and atrioventricular dissociation due to either complete or advanced atrioventricular block, but without associated cardiac malformations. Two patients were siblings of a previously reported case of congenital heart block.

Symptomatology was generally minimal or absent, though one case had severe diffi-

culties during the first month of life. There was a systolic murmur present in all cases, and a diastolic murmur in a minority of cases. Mild cardiomegaly and normal pulmonary vasculature were the usual roentgenographic findings. The QRS complexes in the electrocardiograms were all of the supraventricular type. In several cases, left ventricular hypertrophy was evident.

Right heart catheterization revealed mild elevation in right ventricular pressure in several cases, decreased systemic blood flows, and normal stroke outputs. The latter two findings contrast sharply with the findings of others, and may be due to underestimation of oxygen consumption in the determination of cardiac output. It appears that these patients may respond to increased oxygen demands by the removal of more oxygen per unit of blood, as well as by an increased stroke output.

It seems probable that cases of atrioventricular dissociation due to advanced atrioventricular block are generally interpreted as complete atrioventricular block. It is suggested that the majority of cases of "congenital heart block" probably involve advanced block, and that this may account partly for their good prognosis.

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Case Reports

Thallium Poisoning

Report of Two Cases

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A survey of the admissions to the Cook County Hospital, Chicago, for the five-year period from 1954 to 1958 reveals that in a total of 396,220 admissions (excluding psychiatric cases) only two cases of thallium poisoning were recognized. While thallium poisoning is not common, neither is it so rare that it should be seen only twice in 396,000 admissions to a hospital catering to the less privileged classes. This suggests that its clinical manifestations are at times confusing and that it may simulate other conditions. The suspected diagnosis can be confirmed only by biochemical analysis. It is not the purpose of this paper to review the literature regarding thallium poisoning, but rather to add two patients whose presenting sign was ataxia. We wish to point out the salient features and the possible sources of diagnostic confusion and to report on the use of dimercaprol (BAL) and trihexyphenidyl (Artane) in therapy of thallium poisoning. For a more complete review of the recent American literature, the reader is referred to an article by Grossman.[1]

Report of Cases

CASE 1.—*A 4-year-old boy with alopecia, ataxia, and tremor. Thallium poisoning confirmed by chemical test. Rapid response to treatment with dimercaprol. Trihexyphenidyl used to control tremor.*

Submitted for publication Dec. 18, 1958.

From the Children's Neurology Service of the Cook County Hospital and the Department of Pediatrics of Northwestern University. Aided in part by grants from United Cerebral Palsy and Muscular Dystrophy Association, Chicago.

A 4-year-old Negro boy was admitted to the Cook County Children's Hospital on Oct. 11, 1957, because of an unsteady gait, "shakiness," tremulous speech, and lethargy of two days' duration. In addition, some loss of hair had been noted. Except for a mild upper respiratory infection associated with vomiting in the preceding week, the child had been well. The possible ingestion of fruit sprays, pesticides or rodenticides, mercurous chloride (Calomel), or other compounds containing lead, arsenic or other poisonous substance was denied by the mother. Past, personal, family, and social histories were noncontributory.

He was a physically normal 4-year-old boy weighing 40 lb., somewhat lethargic, but with normal temperature, pulse, respiratory rate, and blood pressure, and with a slightly injected pharynx. The pertinent physical findings included a moderately severe, generalized alopecia involving the entire scalp except for the frontal areas. The eyebrows and the eyelashes were also spared. The soles and palms were thickened uniformly and were somewhat hyperkeratotic. The gait was extremely ataxic, although independent walking was still possible. An intention tremor, most pronounced in the upper extremities was present with the patient in both the erect and the supine position. Speech evinced tremulousness and a loss of cadence. End-position nystagmus on lateral gaze and a positive Romberg test were the only other abnormal findings. Knee jerks were present and were bilaterally equal.

Laboratory tests were all normal. These consisted of serologic tests for syphilis; tuberculin testing; throat culture; x-rays of skull, long bones, and chest; carbon dioxide test for sickling; hemoglobin electrophoresis; erythrocyte sedimentation rate; antistreptolysis-O titer; cerebrospinal fluid chemistry, cell count, and culture. Leukocyte count on admission was 4,900 per cubic millimeter, with 75% polymorphonuclear cells, 25% lymphocytes. When repeated two days later, there were 7,400 cells per cubic millimeter, with 49% polymorphonuclears and 51% lymphocytes. Admission urinalysis revealed 2+ proteinuria and clumps of leukocytes.

Diagnosis at this time was acute cerebellar ataxia of unknown etiology. A possible intracranial neoplasm could not be ruled out. The patient was given procaine penicillin for the pharyngitis and sulfisoxazole (Gantrisin) for the urinary infection, both of which cleared up promptly. However, the alopecia and ataxia became progressively worse, and two weeks later the patient was no longer able to walk alone. The speech impediment became progressively severer until speech was entirely lost. There was no evidence of increased intracranial pressure. The possibility of a toxic cerebellar encephalitis due to poisoning by lead, arsenic, mercury, or thallium was considered. The absence of a history of exposure to lead, of basophilic stippling of the erythrocytes, and of coproporphyrin in the urine, and the lack of a heavy metal line in the x-rays of the long bones, were points against the diagnosis of lead intoxication. The hyperkeratosis of the palms and soles suggested arsenical poisoning, and the alopecia pointed to thallium toxicity. Accordingly, urine and blood were sent for qualitative chemical analysis on Oct. 25, 1957, two weeks after admission. Because the patient continued to get progressively worse, treatment with dimercaprol was begun empirically on Oct. 28, seventeen days after admission, in a dose of 2.5 mg/kg/day intramuscularly in four divided doses. In spite of the dimercaprol therapy, the patient continued to do poorly. Within three days the tremor had become so severe that the child was unable to sit up in bed unaided. In the absence of a report on the chemical examination of blood and urine, and with the feeling that additional drug therapy might control the severe tremors, trihexyphenidyl was administered, 2.5 mg. t. i. d. and the dose of dimercaprol was doubled to 5 mg/kg/day in divided doses. There was immediate and dramatic improvement within three days. The gross tremors and ataxia had improved to the point that the patient was again able to walk and feed himself. Within 10 days the ataxia, tremor, and lethargy disappeared entirely. Injections of dimercaprol were stopped on Nov. 13, 1957, after a total of 16 days of therapy. Trihexyphenidyl was continued for another week, until Nov. 20, 1957, at which time the patient's speech had resumed its normal quality. Approximately one week later, beginning regrowth of hair was noted. The child was discharged on Dec. 3, 1957, after a seven-week hospitalization, as clinically cured.

The results of the toxicological studies done on the urine and blood, which became available approximately one week after the beginning of the dimercaprol therapy, confirmed the suspected diagnosis of thallium poisoning.

The concentration of thallium in blood and urine at the height of the clinical disturbance, Nov. 1, was high. By the end of the dimercaprol treatment period, on Nov. 14, the blood concentration had dropped moderately, but the urine excretion continued at a high level. Three weeks after the conclusion of therapy with dimercaprol, when the patient was clinically symptom-free, the concentration of thallium in blood and urine had dropped much further. Unfortunately, the patient failed to return for follow-up studies as requested.

TABLE 1.—*Special Toxicologic Studies*

Date	Blood	Urine	Remarks
Oct. 25	Thallium ++++	Thallium ++++	Negative for lead, arsenic, and mercury; start of dimercaprol Rx
Nov. 1	800μg. %	750μg. %	Tremor and ataxia, most severe; trihexyphenidyl started
Nov. 14	605μg. %	650μg. %	End of dimercaprol therapy
Dec. 4	350μg. %	88μg. %	Three weeks after stopping dimercaprol therapy

CASE 2.—*A 3-year-old boy with known athetoid cerebral palsy developed alopecia, ataxia, and tremors. Thallium poisoning confirmed by laboratory test, successfully treated with dimercaprol. Trihexyphenidyl used to control tremor.*

A 3-year-old white boy had been followed in the outpatient clinic with a diagnosis of athetoid cerebral palsy due to kernicterus. The athetosis was of a moderate degree. On Jan. 3, 1958, after an absence of six months from the outpatient clinic, the patient returned because of an unsteadiness in gait which had been getting progressively worse for the past four months. Repeated questioning failed to elicit a history of ingestion of lead, arsenic, thallium, or other toxic compounds. There was, however, a history of pica. In addition, there was a history that the patient and two of his siblings were being treated for alopecia due to "ringworm" of the scalp.

The increasing difficulty in walking was interpreted as being due to an ataxia superimposed on the previously existing athetosis. In addition, there was a biparietal alopecia. Laboratory work revealed a mild hypochromic, microcytic anemia, a white blood cell count of 11,700, with 31% polymorphonuclears, 52% lymphocytes, 5% monocytes, and 11% eosinophils. No basophilic stippling was noted. Urinalysis was normal. A tentative diagnosis of thallium poisoning was made, and specimens of blood and hair cuttings were sent to the laboratory for chemical analysis. Within a week, the following report was returned:

	Hair	Blood
Arsenic	0	0
Lead	0	10μg. % (normal)
Thallium	318μg. %	102μg. %

The diagnosis of thallium poisoning was thus confirmed.

Unfortunately, the patient did not return to the clinic at his next appointment and dropped out of sight for another seven months. He returned for hospital admission on Aug. 10, 1958. At this time, it was reported by the parents that the alopecia and ataxia had spontaneously resolved and that he had been in good health. However, on the day before admission, he had suddenly stopped walking. At this time there was no alopecia, but the child was irritable and refused to stand or walk, for no apparent reason. Two days after admission, he began to walk, but with a broad-based, ataxic gait. At this time, marked intention tremors of the extremities were noted. The ataxia and tremors increased, and on Aug. 18, 1958, eight days after admission, a patchy alopecia in the parietal areas appeared. Dimercaprol, in a dose of 5 mg/kg/day in four divided IM doses and trihexyphenidyl 2.5 mg. three times daily were administered. There was rapid improvement with a complete disappearance of the tremors, ataxia, and irritability within four days. Therapy was stopped after six days, and the child was discharged as well.

There were no changes from his previous hemogram; urinalysis was normal; there was no coproporphyrinuria, and x-rays of the long bones were normal.

Blood thallium on Aug. 18, 1958, was 150μg. %; on Aug. 30, 1958, it was 80μg. %. The two older siblings who were reported to have "ringworm" in January, 1958, also had laboratory evidence of thallium poisoning, with blood levels of 50μg. % in one and 100μg. % in the other. The siblings had no clinical complaints except that of alopecia. The source of thallium intoxication in the family was never identified.

Comment

Sabouraud observed epilation after thallium was given orally for the treatment of dysentery, and it was this property which promoted its early use for epilation in the treatment of ringworm of the scalp. Epilation also followed its topical use, and this toxic effect was pointed out by Munch,[2] who reported the treatment of 8,006 cases of ringworm of the scalp, with 447 poisonings (5.5%) and 6 deaths. Because of its toxicity, the use of thallium as a therapeutic agent has been stopped in this country. It is now widely used as a rodenticide or pesticide. Munch[2] reported a group of cases of thallotoxicosis in California following the inadvertent use of "Thalgrain" (1% thallium sulfate) in making tortillas.

TABLE 2.—*Blood Thallium*

	Patient	Sibling 1	Sibling 2
1/ 3/58	102μg. %	--	--
8/18/58	150μg. %	50μg. %	100μg. %
8/30/58	80μg. %	--	--

Thallium is absorbed through the gastrointestinal tract or the intact skin and is distributed to the muscles, spleen, and kidneys, hair, and all body fluids. For adult humans, the LD_0 is between 0.2 and 1.0 gm.[4] For the child, it is considerably less.

The symptomatology of thallium poisoning varies with the acuteness of the intoxication. In the acute cases, the first symptoms are those of a hemorrhagic gastroenteritis, often within 12 to 14 hours[5] associated with salivation, lacrimation, sweating, generalized myalgia, headache, tachycardia, dyspnea, precordial constriction, and hypertension.[6] Symptoms simulating an acute respiratory infection, such as our first patient had, may be due to bronchial edema or bronchopneumonia, which have been reported at autopsy.[3]

If the patient survives for two to five days, neurologic symptoms such as our patients exhibited may appear.[5,7] Paresthesias and other evidences of peripheral neuritis may occur, the lower extremities being involved more frequently than the upper. Alopecia usually involves the entire scalp with the exception of a small strip in the frontal area. Facial hair and eyebrows are also spared. The alopecia is reversible, unless sclerosis of the hair follicles occurs. The selective distribution of the alopecia has been related, though not satisfactorily, to the fact that the hair of the frontal area of the scalp is said to be innervated by spinal nerves without sympathetic components, but that the remainder of the scalp and body hair is said to have a sympathetic innervation.[7-9] Keratinization of the palms and soles and trophic disorders of the nails have also been de-

scribed[5] similar to those which occur in arsenic poisoning.

In chronic thallium poisoning, neurologic symptoms are prominent. Paresthesias, deliria, convulsions, and coma may occur. Cranial nerve involvement may cause ptosis, strabismus, facial palsies, mydriasis, retrobulbar neuritis, and even optic atrophy with blindness.[5] Ataxia may be the presenting symptom as it was in our two patients. Achlorhydria,[10] psychoses, and permanent kidney damage have also been reported.[4]

The reports on the treatment of acute thallium poisoning indicate that it is very unsatisfactory and largely nonspecific, consisting of the use of gavage, analgesics, sedatives, fluids, maintenance of nutrition, and physiotherapy for late complications. The use of chemical antidotes has not been very successful. The intravenous administration of iodides to convert the toxic thallium to a nontoxic insoluble iodide, which is then gradually eliminated after reconversion by sodium thiosulfate, has been abandoned as ineffective.[3] Since various chelating agents have been used successfully in arsenic, lead, and mercury poisoning, it would be natural that these would be tried in thallium poisoning. Of the various chelating agents available, dimercaprol appears to be the most effective.* The theoretical basis for the use of dimercaprol is that a toxic metabolite is produced in thallium poisoning, as in other heavy metal poisonings, which combines with and is deactivated by dimercaprol.[11] Longcope and Luetscher[12] found no experimental evidence for the efficacy of dimercaprol in induced thallium poisoning in animals. Grossman[1] postulated that the failure of dimercaprol in the treatment of thallium poisoning could be due to its use late in the course of the disease, for the success of dimercaprol treatment of other heavy metal poisoning seems to be closely related to its early administration. Some authors[6,11,13] found dimercaprol to be ineffective when used in a dose of 1.5 to 2.5 mg/kg/day and others,[14] using a dose of 3 mg/kg/day for a short period of time, found an aggravation of symptoms. This was also our experience when using a dose of dimercaprol of 5 mg/kg/day in Case 1, and it was this aggravation of the neurologic symptoms which prompted us to add trihexyphenidyl to the treatment regimen. In Case 2, despite the same dose of dimercaprol, no aggravation of symptoms was observed. It has been reported[15,16] that a dose of 5 mg/kg/day of dimercaprol will cause toxic reactions, such as pains, paresthesias, blepharospasm, perspiration, lacrimation, salivation, nausea and vomiting, restlessness, apprehension, and weakness which last for a period of one to two hours, but none of these were noted in our patients.

Trihexyphenidyl was used in our first patient, empirically, in an attempt to control the tremors which had become so prominent that the patient was unable to walk or feed himself. Trihexyphenidyl resembles atropine in that it depresses salivation, dilates the pupils, and stimulates the cerebrum, but it has no effect on the heart rate, blood pressure, or circulation.[17] It has been found to be effective in disease of the extrapyramidal system, particularly Parkinsonian tremors and rigidity.[18,19]

In both cases, we empirically gave a dose of trihexyphenidyl of 2.5 mg. three times daily. There was a striking, immediate reduction of the tremors, which could hardly be explained by the concurrent administration of dimercaprol. It was felt that the rapid diminution of the tremors, which preceded the lessening of the ataxia, was at least in part due to the specific effect of trihexyphenidyl. This rapid clinical improvement in the tremors suggests that the neurophysiologic and morbid anatomic basis for the tremors of thallium poisoning and of Parkinsonism may be similar. In fact, extensive changes in the central nervous system have been described in acute thallotoxicosis. Chromatolysis of neurons, espe-

* At the time these patients were seen, we were unfamiliar with the use of a newer chelating agent, Dithizon® (diphenylthiocarbazone).

cially of the pyramidal tracts, third nucleus, substantia nigra, and of the pyramidal cells of the globus pallidus are common,[3] as well as gliosis of the dentate nucleus of the cerebellum.[20] The involvement of the substantia nigra in both thallotoxicosis and Parkinsonism suggests a common basis for the tremors and for their favorable response to trihexyphenidyl in both conditions.

The diagnosis of chronic thallium poisoning is based on a history of the ingestion of the offending agent, together with alopecia limited to the scalp but sparing the frontal area, and on the neurologic symptoms of ataxia, tremor, and/or peripheral neuritis. Gastrointestinal and respiratory symptoms may precede or accompany the other symptoms, and palmar and plantar keratotis may occur. The specific diagnosis can be made only by chemical tests.

In our patients, in whom ataxia and tremors were outstanding early signs, other causes had to be considered. Cerebellar ataxia due to other causes can be ruled out by the absence of alopecia, by a slower onset, and by other localizing signs produced by the causative lesion, e. g., brain tumor or encephalitis. Ataxia due to peripheral nerve lesions can be readily distinguished by the absence of alopecia and the selective predominance of either motor or sensory symptoms, decreased deep tendon reflexes, paresthesias, the absence of other signs of cerebellar involvement, electromyographic signs of lower motor neuron involvement, and the occasional response to a therapeutic test with vitamin B_1. Labyrinthitis can be ruled out by the use of labyrinthine or postural tests.

Chronic poisonings with other heavy metals may have many points of similarity which might make differential diagnosis difficult, particularly in young children and infants, in whom the predilection for bizarre and widespread neurologic symptoms are commoner. Nevertheless, some of the distinguishing clinical signs of heavy metal intoxication are given in Table 3.

TABLE 3.—*Symptomatology of Subacute and Chronic Heavy Metal Poisoning in Children*

Findings	Lead	Arsenic	Mercury	Thallium
Ataxia	++	+	++	++++
Convulsions at onset	++++	+++	—	—
Peripheral neuritis				
Motor	+*	+	++	++
Sensory	—	++	±	+
Alopecia	—	±	±	++++
Gastrointestinal	++	+	++	+
Palmar and planter keratosis	—	+++	—	+
Basophilic stippling of RBC	+++	+	+	±
Albuminuria	+	+	+++	+
Coproporphyrinuria	++++	—	—	—
Metal line in bones	++++	+	+	+
Metal found in hair and nails	—	++++	—	++

* Peripheral nerve palsies (so commonly seen in adults) are not common in children.

Summary

Thallium poisoning must be considered in any bizarre disease with central nervous system symptoms and alopecia. In our two cases, progressive ataxia and tremors were the presenting signs. Moderate doses of dimercaprol appear to be effective in achieving detoxification. Trihexyphenidyl (Artane) was effective in relieving the tremors, which were a prominent feature.

Eleanor Berman, Ph.D., toxicologist, Illinois Masonic Hospital, Chicago, performed all the heavy metal determinations.

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Primary Carcinoma of the Liver in Infancy

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Primary carcinoma of the liver in infancy and childhood is of relatively rare occurrence. Steiner,[7] Bigelow,[1] and others [5] have reviewed the literature on the subject and reported cases of their own. It seems that many of the reported cases cannot be classified with accuracy as being real primary malignant carcinomas of the liver. Steiner [7] considered that of the 105 cases previously reported in patients under 16 years of age, only 75 presented evidence justifying the diagnosis. We thought it would be of interest to report a case of liver tumor encountered in an 8-month-old white girl which we believe is a primary hepatic carcinoma.

Report of Case

An 8-month-old white girl was admitted to the hospital because of poor gain of weight, a hypochromic anemia, and the presence of an intra-abdominal mass.

The mother was multiparous. The pregnancy and delivery were uneventful. The baby appeared normal until the age of 5 months, when the curve of weight became stationary. This was associated with anorexia and profuse diaphoresis. At 6 months she became pale, blood examination revealing a hemoglobin of 10.5 gm. % with a red cell count of 3,430,000 per cubic millimeter. Despite therapeutic administration of iron the anemia persisted. At the age of 8 months, approximately 10 days prior to admission to the hospital, her abdomen became distended and tense.

Physical examination revealed an 8-month-old white girl weighing 6,225 gm. and measuring 66 cm. in length. The patient appeared weak and malnourished. There was no fever. The skin was pale, with decreased subcutaneous fat. There was increased collateral venous circulation over the abdomen. There was no jaundice. The abdomen was distended and tense, but it was possible to palpate an intra-abdominal mass occupying the right upper quadrant and part of the right lower. The surface of the mass was nodular and the consistency was solid. It could be displaced laterally and it also followed the diaphragmatic movements. An abdominal roentgenogram showed displacement of the transverse colon downward and of the stomach toward the left by a soft tissue shadow which occupied the total right upper quadrant and part of the right lower. Small irregular calcifications were seen within the abnormal shadow.

Laboratory Examinations.—Urinalysis: albuminuria of 0.45 gm. % and increased urobilin. Blood: red blood cells, 3,000,000 per cubic millimeter; hemoglobin, 8.8 gm. %; leukocytes, 17,000 per cubic millimeter; serum bilirubin (total): 0.7 mg. %.

After intensive preoperative preparation an exploratory laparotomy was performed. The left lobe of the liver was the site of a tumor mass measuring 15 by 12 by 8 cm. The surface was nodular and yellowish in color. Through a long right transrectal incision the tumor was found occupying the greater part of the upper abdomen and part of the lower right. The falciform ligament was sectioned, permitting the observation of the upper aspect of the left lobe; the left triangular ligament was also sectioned, freeing the left lobe containing the tumor. Dissection was started on the anterior aspect and continued through to the posterior border of the liver in normal tissue. Blood vessels were tied carefully and also the openings of the biliary ducts; the section was done leaving an angle of tissue that permitted later suture attaching the falciform ligament over the cut surface. Absorbable gelatin sponge (Gelfoam) was included in the suture to overcome oozing. Careful exploration of the abdominal cavity revealed no other site of tumor. The incision was closed in layers with chromic absorbable sutures and silk for the skin.

The specimen was sent for examination to the Department of Pathology, Hospital San Juan de Dios, Santiago.* The report from the pathologist (Dr. M. Ossandon) was as follows:

Macroscopic Examination.—The tissue specimen consisted of a large mass corresponding to the left lobe of the liver. It measured 15 by 12 by 8 cm. The surface was yellow-greenish and distorted by numerous nodular protuberances of variable sizes.

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From Chile Exploration Co. Hospital. Former Fellow in Pediatrics, Mayo Foundation, Rochester, Minn. (Dr. Koch). Chief of Staff, Chile Exploration Co. Hospital (Dr. Bradford).

* University Hospital.

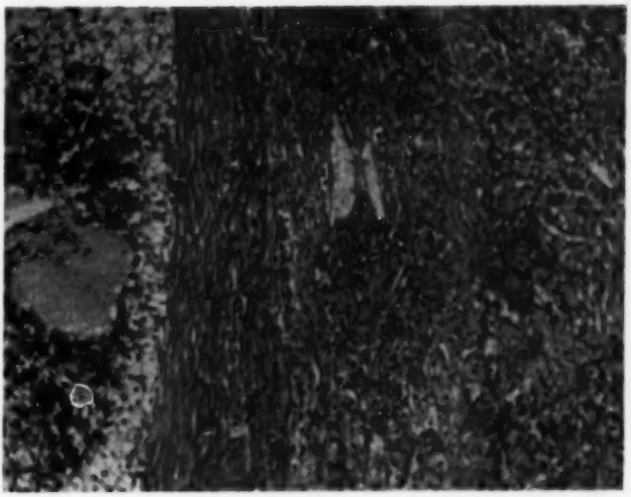

Fig. 1.—Microscopic section showing a band of connective tissue separating an area of hepatic parenchyma of normal appearance from a nodule formed by malignant cells.

On section, the surface of the mass showed that normal liver parenchyma was replaced by abundant confluent nodules of different sizes, the surfaces of which were yellowish, containing hemorrhagic and necrotic areas. The nodules were separated by irregular bands of connective tissue dividing the tumor in a lobular-like arrangement. The tumor was not encapsulated.

Microscopic Examination.—Some areas of normal hepatic tissue were present, but most of the sections showed a great degree of infiltration of neoplastic tissue. The neoplasm was made of numerous confluent nodules surrounded by fibrous stroma (Fig. 1). Most of the neoplastic cells appeared epithelial in character, tending to resemble hepatic parenchymal cells. They were polygonal in shape, with a central hyperchromatic rounded nucleus. In some cells the cytoplasm was rather scanty, faintly granular, and deeply stained (Fig. 2). In others, the cytoplasm was larger, vacuolar, and slightly stained (Fig. 3). Mitotic figures were not frequent. The neoplastic elements were arranged in solid and cord-like groups. The cords were separated by endothelium-lined spaces. Occasionally the cells showed a tendency to tubular arrangement. It was of interest to note that in some areas the stroma, which was not too abundant, had undergone osteoid changes. Scattered throughout the tumor there were zones of hemorrhage and necrosis. Neoplastic cells were also encoun-

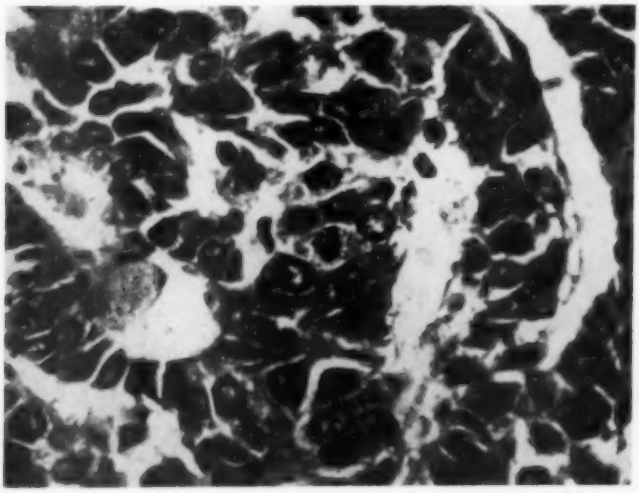

Fig. 2.—High-power view of malignant cells with granular and deeply stained cytoplasm.

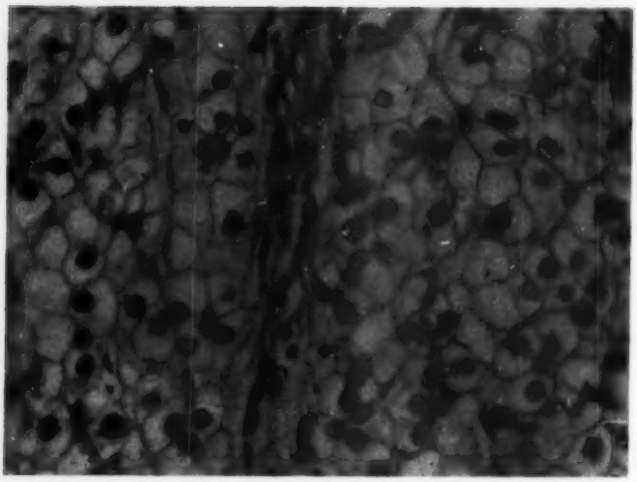

Fig. 3.—High-power view of malignant cells with clear cytoplasm.

tered in the lumen of many hepatic veins, invading part of the capsular tissues and infiltrating zones of normal parenchyma.

Pathological diagnosis: primary carcinoma of the liver (Grade 1 of Broders' classification), with intravenous invasion.

Comment

Primary malignant neoplasms of the liver in infancy and childhood are less frequent than secondary ones. Hepatic metastases may arise from a variety of tumors but apparently more frequently from a neuroblastoma.[3]

Primary hepatic carcinomas are more frequent under 2 years of age in the pediatric group. It is possible that it can develop during fetal life as it has been reported at birth.[4] Singleton[6] has reported a case in a 17-day-old baby. According to Steiner,[7] carcinoma of the liver is more frequent among boys (53.2%) than among girls. In an infant the most frequent clinical findings are disturbance in nutrition, anemia, and the presence of a fast-growing intra-abdominal tumor located in the right upper quadrant. In older children abdom-

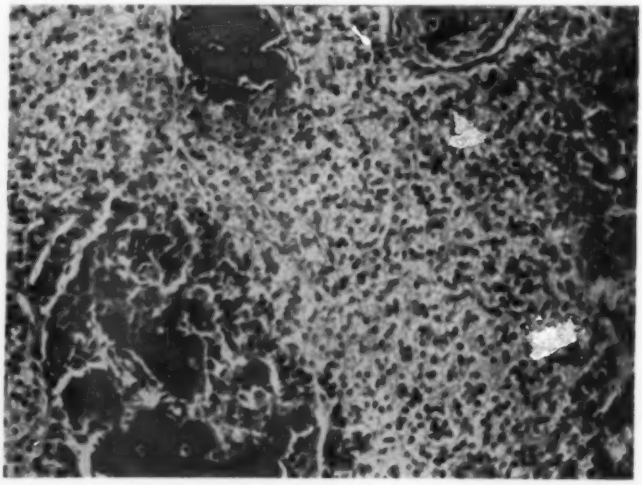

Fig. 4.—Microscopic section. Low-power view of neoplastic tissue. Focal areas of calcified osteoid tissue are seen within the section.

inal pain is a frequent symptom. Jaundice is rare, occurring in 6.5% of the cases reviewed by Steiner.[7] Average duration of life after appearance of the first symptoms is about four months. Metastases usually are present in one-third of the cases, being more frequent in the lungs. They also may occur in lymph nodes, pleura, pericardium, spleen, and pancreas.[7] From the pathological point of view, carcinomas of the liver may be classified into hepatomas, or carcinomas of the liver cell, and cholangiomas, or carcinomas of the bile-duct cell. This last form is less frequent. Evidence of bile formation may be present in some hepatomas. Accurate identification of these two types sometimes is difficult.

The histopathological findings and the clinical evolution of our case support the diagnosis of primary hepatic carcinoma. The history of malnutrition, anemia, and the presence of a fast-growing intra-abdominal mass suggested in the beginning that this infant had a malignant neoplasm. Wilms tumor, neuroblastoma, and teratoma were considered the best diagnostic possibilities prior to laparotomy, inasmuch as they are the most frequent malignant abdominal tumors in infancy. Nevertheless, suspicions were aroused that the mass might be related to the liver after the abdominal film revealed displacement of the intestines by a soft tissue shadow which appeared fused with the hepatic shadow. Laparotomy gave the answer when the tumor was found in the left lobe of the liver. Indications of malignancy were the size and rate of growth of the tumor, the invasive character of the neoplastic cells into normal hepatic parenchyma, stromal tissues, and blood vessels. Histologically, the malignant cells appeared epithelial in origin, derived most likely from hepatic elements and not from the mesenchyma. There was not much variation in the size of the nuclei of the neoplastic cells, and mitoses were rather scant. It was of interest to encounter focal osteoid calcified areas in the stroma of the tumor, similar to a case reported by Bigelow and Wright,[1] which was considered a mixed or teratoid type of hepatic carcinoma.

In general, the appearance of the tumor encountered in our case was that of a differentiated carcinoma of the liver (Grade 1 of Broders' classification). Pulmonary metastases appeared four months after surgery.†

Summary

A case of primary hepatic carcinoma in an 8-month-old white girl is reported. Symptoms appeared at the age of 5 months; they included malnutrition, anemia, and a fast-growing intra-abdominal mass. On laparotomy the tumor was found in the left lobe of the liver. Partial hepatectomy with total extirpation of the tumor was performed. Histopathological studies supported the diagnosis of differentiated primary hepatic carcinoma. The stroma of the neoplasm showed areas of calcified osteoid tissue. Pulmonary metastases appeared four months after surgery.

Chile Exploration Co. Hospital.

† At the time of submitting this paper for publication the patient has been alive for 13 months after surgical removal of the hepatic tumor.

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Primary Aldosteronism Due to Adrenal Hyperplasia

Occurrence in a Boy Aged 10 Years

BERNARD THERIEN, M.D.; RAYMOND C. MELLINGER, M.D.; JOHN R. CALDWELL, M.D., and PHILIP J. HOWARD, M.D., Detroit

Since Conn's description of the clinical features associated with primary aldosteronism in 1955,[1] several other cases have been reported in the literature.[2-12] This syndrome, which is the result of hypersecretion by the adrenal gland of the mineralocorticoid hormone aldosterone, is usually due to a functioning adrenocortical adenoma. In the few cases without adenoma, hyperplasia chiefly involving the zona fasciculata has been found,[9] and hyperaldosteronism due to adrenocortical carcinoma with hepatic metastases has been reported.[4] All patients were adults except one girl [6] aged 13, and one boy [12] aged 9 years.

The clinical syndrome originally described by Conn [1,13] consists essentially of polyuria and polydipsia, arterial hypertension, periodic weakness and "paralyses," paresthesiae, and intermittent tetany. These findings are associated with altered electrolyte metabolism manifested by metabolic alkalosis with hypokalemia and hypernatremia, and elevated potassium content of sweat, saliva, and urine, with low sweat, salivary, and urinary sodium (Table 1).

The purpose of this paper is to report a case of primary hyperaldosteronism occurring in a 10-year-old boy who had been thought to have "essential" hypertension for many years. It is postulated that this case may represent an unusual form of congenital adrenal hyperplasia.

Henry Ford Hospital.

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TABLE 1.—*Clinical and Biochemical Features of Primary Hyperaldosteronism*

Clinical Data	
1 Polyuria, polydipsia	
2 Arterial hypertension	
3 Alkaline urine	
4 Impairment in urinary concentrating capacity	
5 Periodic weakness and "paralyses"	
6 Lack of edema	
Biochemical Data	
1 Serum pH: alkalosis	
2 Serum potassium: low	
3 Serum sodium: high	
4 Sweat, salivary, and urinary potassium: high	
5 Sweat, salivary, and urinary sodium: low	
6 High urinary aldosterone	
Cause	
Adrenocortical tumor	
Hyperplasia (childhood)	

Report of Case

A Negro boy (Fig. 1) aged 9 years and 10 months was first seen in the Pediatric Clinic in 1952, when he was 5 years old. Although he was brought to the clinic for treatment of a simple upper respiratory infection, the past history disclosed three significant symptoms: frequent daily headaches, polydipsia, polyuria and enuresis. The patient had been complaining intermittently of headache ever since he began to talk at the age of 3 years. The headaches were apparently severe, but information as to the mode of onset, the site, and any associated symptom, was not clear. The polydipsia was also very severe. The child awoke three or four times each night to drink two or three glasses of water each time, and during the day he drank two to three quarts of milk in addition to many glasses of water. The polyuria was proportional to the polydipsia, and enuresis was still present nightly. These symptoms persisted during the subsequent five years of observation.

The child had had three convulsive episodes during his second year of life, all associated with high fever. Both parents and two siblings were alive and well. There was no history of hypertension in any other member of the family.

When first examined in the Pediatric Clinic in 1952, the child was somewhat mentally and physically retarded, being approximately 5.5 kg. underweight for his height and age. The blood pressure was 230 mm. Hg systolic and 140 mm.

Fig. 1.—Photograph of the patient on the sixth postoperative day. It shows curvilinear epigastric incision. Note absence of virilism or physical evidence of puberty.

Hg diastolic; there was spasm of the retinal arterioles, and a Grade I basal systolic heart murmur. The remainder of the examination was considered normal. The patient was admitted to the hospital for evaluation of this severe hypertension. His blood pressure ranged from 160 to 200 mm. Hg systolic and 115 to 140 mm. Hg diastolic with one reading of 300/190 recorded (Fig. 2).

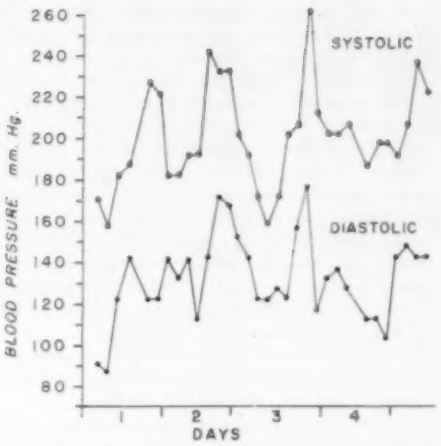


Fig. 2.—Daily preoperative blood pressures.

The response to three phentolamine (Regitine) tests and one piperoxan (benzodioxane; Benodaine) test were normal. The presence of strong femoral pulses and consistently elevated blood pressure in the legs ruled out the possibility of coarctation of the aorta. There was no evidence of glomerulonephritis, since repeated urinalysis failed to demonstrate albuminuria, hematuria, or pyuria. However, the presence of polyuria was established during the first hospital stay with the specific gravity of the urine varying from 1.004 to 1.006. The failure of the polyuria and the hyposthenuria to respond to vasopressin (Pitressin) administration excluded the possibility of diabetes insipidus due to antidiuretic hormone deficiency. There was no clinical, radiologic, or electroencephalographic evidence of an intracranial lesion. At no time was there glycosuria, and the oral glucose tolerance was quite normal. Chest x-ray demonstrated left ventricular hypertrophy, but an electrocardiogram was not done. The total direct eosinophil count was 272 with a 66% fall four hours after the intramuscular administration of 25 units of aqueous corticotropin (ACTH).

On the basis of the hypertension, the history of convulsive seizures, some mental retardation, and the history of episodic perspiration, the diagnosis of diencephalic epilepsy was entertained. Several electroencephalograms failed to demonstrate any compatible abnormality, however, and the subsequent course of the disease, including the lack of response to anticonvulsive medication, failed to support this diagnosis.

In May, 1953, the patient was readmitted to the hospital with increasingly severe symptoms of headache, polydipsia, polyuria and enuresis. Repetition of the previous studies failed to demonstrate the cause of the disorder. Therapy with hexametho-

nium was initiated with some improvement in the number of headaches, but with no significant reduction in the blood pressure.

In December, 1955, the patient was admitted to the hospital for treatment of an upper respiratory infection. Following his recovery, tonsillectomy and adenoidectomy were accomplished without incident. There had been no significant change in the patient's primary condition. Treatment with hydralazine and reserpine was initiated and continued until the most recent hospitalization. Although this treatment seemed to be beneficial, the patient's blood pressure remained at very high levels. On two occasions, he was admitted to the emergency ward because of headache, hypertension, and vomiting, with a question of hypertensive encephalopathy or cerebral vascular accident. These episodes were transient and left no sequelae.

During the five years of observation and treatment, the patient's urine had never given an acid reaction. The urinary specific gravity had never been above 1.007, except during a concentration test when it reached 1.009 (Table 2).

TABLE 2.—*Renal Function Studies*

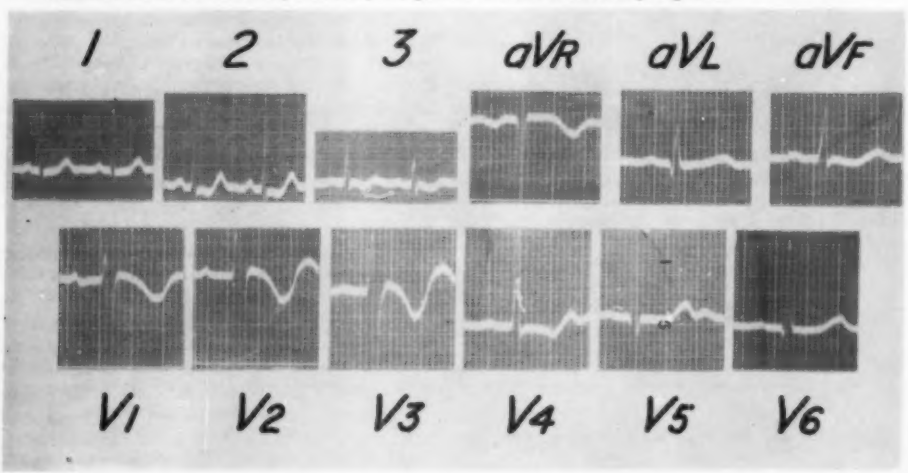
Date	Specific Gravity of Urine	Reaction of Urine	PSP (1 Hr.), %	Urea Clearance Standard Cc/Min.	NPN Mg. %	IVP
1952	1.004	Alkaline	55	38	37	N
1953	1.005	Alkaline	..	43	25	—
1954	1.006	Alkaline	20	36	32	N
1955	1.001	Alkaline	34	..	30	—
1957	1.001	Alkaline	42	34	44	N

The most recent and seventh hospital admission occurred in July, 1957. In addition to the usual complaints of headache, polyuria, polydipsia and enuresis, the patient had experienced generalized myalgia, although there had been no muscle weakness.

Upon examination the boy weighed 26.8 kg. and his height was 135.9 cm. His weight curve, plotted on an Iowa University weight grid since the age of 5 years, was found to follow consistently the 16th percentile. His blood pressure was 240 mm. Hg systolic and 180 mm. Hg. diastolic. Pulse was 108 per minute. Fundoscopic examination revealed some arteriolar constriction, the artery/vein ratio being approximately 1:4. There were no exudates or hemorrhages. The heart was slightly enlarged to percussion, and there was a mild systolic murmur at the apex. The physical examination was otherwise within normal limits. There was no physical evidence of puberty, and certainly no clinical stigmata of adrenal virilism or Cushing's syndrome.

Laboratory Examination.—The hemoglobin was 13.8 gm. %, and the white blood cell count was 9,700 per cubic millimeter, with 40% polymorphonuclear neutrophils, 59% lymphocytes, and 1% monocytes. The urine was alkaline; its specific gravity 1.001. It contained no albumin, erythrocytes, sugar, or casts. A urine culture was negative.

Fig. 3.—Particularly in consideration of the patient's age, this electrocardiogram may be considered in the proper clinical context as compatible with, if not diagnostic of, left ventricular enlargement. The evidence, observed best in the unipolar precordial leads, consists of increased positive amplitude and a somewhat delayed inscription time of the RS deflection in leads V4, V5, and V6, together with a ±T wave configuration in these leads. In interpreting the latter one must also take into consideration the possibilities of electrolyte imbalance and digitalis administration. In this case, however, the patient did not receive any digitalis.



In 20 subsequent urinalyses, the specific gravity never exceeded 1.002, and the reaction was always alkaline.

Chest x-ray and fluoroscopy revealed left ventricular hypertrophy, which was confirmed by the electrocardiogram (Fig. 3). Skull x-rays and an electroencephalogram were normal.

Excretion of a test dose of phenolsulfonphthalein was 42% in 60 minutes, and 64% in 2 hours. Standard urea clearance was 34 ml. per minute, and endogenous creatinine clearance was 108 ml. per minute. Nonprotein nitrogen was 44 mg. %, and serum creatinine 0.6 mg. %. Intravenous pyelograms were normal.

The serum electrolytes, measured in a Beckman flame photometer against a standard curve, were as follows: sodium 135, 139, 134 mEq. per liter; potassium 2.1, 2.2, and 3.0 mEq. per liter; chlorides 92 and 95 mEq. per liter, CO_2-combining power of the plasma 27.9, 28.6 mM. per liter; calcium 10.8 mg. %. Venous blood pH, measured by a Beckman pH meter at room temperature, was reported to be 7.47.

The urinary electrolytes were as follows: urinary sodium 116.2, 26.1, 54.2, and 87.0 mEq. per 24 hours on four consecutive days. The urinary potassium on the same days was 55.5, 30.1, 40.7, and 44.0 mEq. per 24 hours. These electrolyte measurements were made while the patient was taking a "normal" diet containing approximately 1.8 gm. of sodium and 2.5 gm. of potassium per day, computed during two days with the aid of a dietetic table.

During the first 31 hospital days, the patient continued to have the same symptoms. His urinary output varied from 3 to 8.3 liters per day, averaging 6.5 liters per day, as measured during a 10-day period of rigid control. His blood pressure, which was checked eight times daily with the patient lying in bed, varied from 125/90 to 260/165 with a 31-day average of 169/111. An intermittent, faint, systolic bruit was noted over the right eyeball, its presence always coinciding with a spike in blood pressure approximately 250 mm. Hg systolic.

During this hospital stay, two additional phentolamine tests were performed using 1 ml. of phentolamine intravenously. The first test produced a fall in blood pressure of 25/20 mm. Hg in two minutes, and the second 30/5 mm. Hg in three minutes. These tests were interpreted as negative. Response to the administration of vasopressin was also measured. Two hours before the test, the patient was given 1,000 ml. of water orally. During the 80 minutes preceding the administration of 0.1 pressor unit intravenously, the urinary output, measured at 15-minute intervals, averaged 8 ml. per minute, and the specific gravity of the urine was consistently 1.001. During the 45 minutes following the vasopressin administration, the urinary output averaged 10.8 ml. per minute, and the specific gravity remained 1.001 in four specimens examined at 15-minute intervals.

TABLE 3.—*Hormone Determinations*

Day	17 OH-CS (Mg/24 Hr.)	17-KS (Mg/24 Hr.)	Creatinine (Mg/24 Hr.)	Volume (Ml/24 Hr.)
Control	25.6	4.6	785	6,250
Control	19.2	8.0	722	4,240
Corticotropin *	45.6	7.2	761	7,195
Corticotropin *	58.2	13.6	842	8,300

Aldosterone in urine
(Dr. Conn): 67 μg/24 hr. (3-day average) (Normal: 4-8)
(Dr. Genest): 27 μg/24 hr. (one day) (Normal: 2-10)
Catecholamines: Normal

* Acthar Gel used, 10 units at 7 a. m. and 10 units at 7 p. m.

Table 3 summarizes the adrenal steroid studies. On four consecutive days, the urinary 17-hydroxysteroids were measured by a modified Porter-Silber reaction,[14] and the 17-ketosteroids by a modified Drekter procedure.[15] After two control days, the patient was given corticotropin in the form of Acthar gel, 10 units subcutaneously at 7 a. m. and at 7 p. m. for two days. The urine collections were made from 7 a. m. to 7 a. m. The 17-hydroxysteroids averaged 22.4 mg. per 24 hours before corticotropin and 51.9 after stimulation. The 17-ketosteroids rose from an average control value of 6.3 mg. per 24 hours to 10.4 mg. per 24 hours after corticotropin administration.

Urine was collected through an indwelling Foley catheter during three 24-hour periods for the quantitative determination of aldosterone. The aldosterone content of these urines, as determined by Dr. Jerome Conn at the University of Michigan, yielded a three-day average of 67 μg. per day (normal, 4-8).[16] During the two days of corticotropin administration, the 24-hour urinary aldosterone level rose to 175 μg. and 96 μg. respectively, representing a twofold increase over control levels, and paralleling the striking increase in the 17-ketosteroid and 17-hydroxysteroid excretion. A similar 24-hour urine sample was analyzed by Dr. Jacques Genest of the University of Montreal. According to Dr. Genest's method,[17] the urinary level of aldosterone was 27 μg. per day (normal 2.2 to 10). The excretion of Compound III and Compound V was also above normal. Dr. Genest's laboratory also determined that the quantities of tetrahydro S, etiocholanolone, and pregnanetriol in these urines were normal.

On the basis of the unremitting severe hypertension, the polyuria, polydipsia, and enuresis, the hyposthenuria not responsive to vasopressin, the metabloic alkalosis, hypokalemia, and low urinary

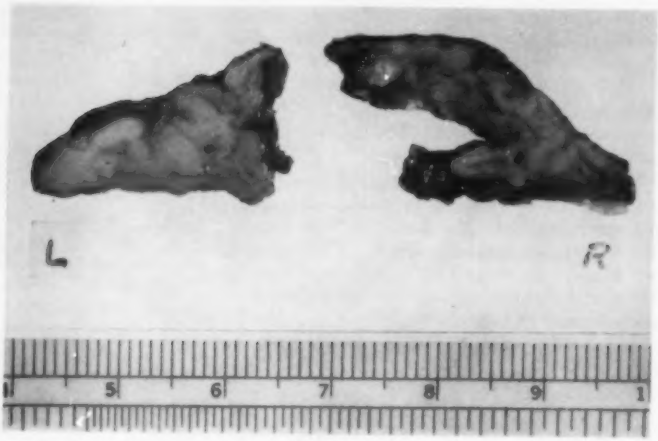


Fig. 4A.—Nodular hyperplasia of cortex of adrenal glands (× 1.5).

Fig. 4B.—Hyperplasia of zona fasciculata (reduced about 37% from mag. × 25).

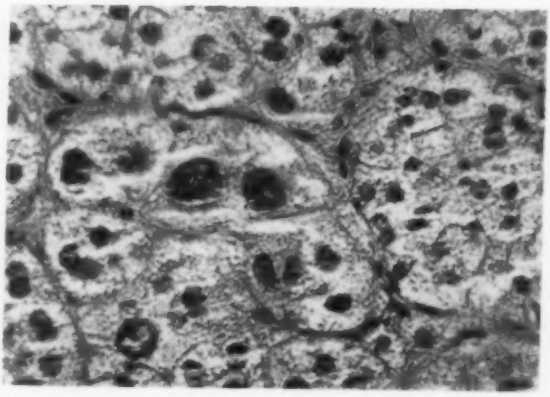


Fig. 4C.—Hyperplasia and nuclear pleomorphism of zona fasciculata (× 375).

sodium, a diagnosis of primary aldosteronism was made, and adrenal exploration was recommended.

The preoperative blood pressure was 200 mm. Hg systolic and 140 mm. Hg diastolic, with the patient receiving reserpine and hydralazine. Preoperative medication consisted of minimal doses of morphine, atropine, secobarbital, and intramuscular hydocortisone. The patient arrived in the operating room alert, awake, and cooperative, but his blood pressure, to the surprise of the anesthetist, was only 110/70 mm. Hg. When he was turned to a right lateral position his pressure declined to 80/40 mm. Hg, and when he was turned to the left lateral position, it fell to 50/0 mm. Hg. After this observation had been repeated several times during the following hour, the operation was postponed for two weeks, during which time no rauwolfia derivatives were administered. On the morning of surgery the patient received 100 mg. of hydrocortisone intramuscularly, and the same premedication he had been given two weeks earlier. There were no further episodes of hypotension immediately preceding surgery. The patient was operated on under general endotracheal anesthesia, with use of ether, nitrous oxide, and intravenous thiopental. A transabdominal approach was elected with a curvilinear epigastric incision extended subcostally on both sides. Both adrenal glands appeared grossly enlarged and were removed in toto. Retroperitoneal exploration revealed no other abnormality. A renal biopsy specimen was obtained from the superior pole of the left kidney. The patient's blood pressure, which fell during the removal of the second adrenal, was supported by the continuous intravenous administration of hydrocortisone and levarterenol.

Pathology.—The right adrenal weighed 8 gm. and the left 8.96 gm. (Fig. 4A). The cortex occupied the major portion of the cross section. It presented a focal nodular hyperplasia, chiefly of the zona fasciculata, which contained many vacuolated, lipid-laden cells, with hypertrophy of the cytoplasm (Figs. 4B, 4C). Kidney biopsy was normal microscopically. There was no tubular hydropic degeneration as reported in previous cases.[9,10,11] Biochemical analysis of the adrenal tissue was performed in Dr. Conn's laboratory. The left adrenal contained 826μg. of aldosterone per kilogram of tissue, and the right adrenal 765μg. per kilogram of tissue.

Course.—The postoperative course was completely uneventful. The blood pressure remained high for the first six days, the period of high-dose steroid administration. It gradually fell, however, to a normal level of 130/85 mm. Hg 16 days after surgery (Fig. 5). By this time, the patient was receiving 0.1 mg. of fludrocortisone (9-α-fluorohydrocortisone; Florinef) once daily, and 5 mg. of cortisone three times daily, his maintenance medication.

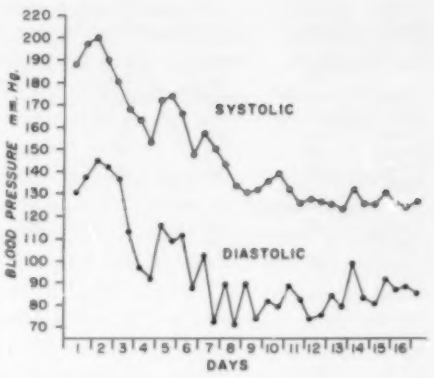


Fig. 5.—Daily postoperative blood pressures.

The serum electrolytes rapidly returned to normal. Nine days after adrenalectomy the potassium was 4.6, the sodium 139, and the chlorides 91.0 mEq/liter. The CO_2-combining power of the plasma remained elevated at 32 mEq/liter. Two weeks after surgery, all serum electrolyte values were well within normal limits, and they have remained normal ever since (Table 4).

The urine volume, which averaged 6.5 liters per 24 hours preoperatively, fell to an average of 2 liters immediately after operation. Two weeks later, it had decreased to 1,200 ml. per day and has since varied between 1,200 and 1,720 ml. daily (Table 4). The polydipsia and enuresis subsided completely. The specific gravity of the urine was 1.011 two weeks after surgery. Despite improved concentrating ability, the specific gravity remains about 1.010. Several urine specimens obtained since operation have given an acid reaction. Although the urinary electrolytes were quite variable in the postoperative period, there was a clear tendency to a high urinary sodium and a low urinary potassium as compared with preoperative figures (Table 4). Two weeks after surgery, the venous blood pH was 7.40.

The patient has felt extremely well during the year since the adrenalectomy. He has had no headache, polyuria, polydipsia, or enuresis. He attends regular school for the first time in his life and enjoys athletics. His blood pressure averages 110 mm. Hg systolic and 65 mm. Hg diastolic. His growth and development are progressing normally. He has noted a craving for salt.

Comment

Primary aldosteronism, an uncommon disorder at any age, occurs quite infrequently in children. Only two patients in

TABLE 4.—*Electrolyte Studies*

Date	Serum Na mEq/L.	Serum K mEq/L.	Serum Cl mEq/L.	Serum CO_2 mM/L.	Blood pH	Urine Vol., Ml.	Spec. Gravity	Urine Na mEq/L.	Urine K mEq/L.
Preop.	135	2.1	92			6,280	1.001	116.2	55.5
Preop.	139	2.2	92	27.9	7.70	4,240	1.001	26.1	30.1
Preop.	134	3.0	95	28.6	7.47	7,195	1.001	84.2	40.7
Preop.						8,300	1.001	87.0	44.0
9/ 3	Adrenalectomy								
9/ 4	149	2.5	97	32.1		2,105			
9/ 5						2,063		105.7	6.8
9/ 6	136	2.3	88	31.2			1.005		
9/ 7						1,960		16.7	11.0
9/ 8						2,460		25.8	16.2
9/ 9	142	2.8	83	37.2		1,920	1.004	44.8	15.8
9/10						2,560	1.003	61.4	22.5
9/11						3,040	1.003	106.8	28.2
9/12	139	4.6	91	32		2,530	1.002	81.7	24.0
9/13					7.40	2,740	1.002	112.3	42.5
9/14						2,660	1.003	125.9	53.2
9/15						2,040	1.005	87.6	26
9/16						1,700	1.011	51.0	23.8
9/17	136	5.6	102	23.5					
9/18						1,200	1.011	84.0	47.4
9/19	138	5.9	99			2,120	1.010	143.0	74.2
9/20	130	5.8	98	20.5					
9/24						1,360	1.006	71.0	29.0
9/25						1,720	1.005	114.0	37.0
9/27	137	4.9	98	21.7					
10/ 1	137	3.4		23.5					
10/ 5	135	4.1	104	25.2					
10/10	136	4.6	99	24.8		1,700			

the pediatric age group have been reported,[6,12] and a third, aged 17 at the time of diagnosis, apparently developed hyperaldosteronism in late childhood.[9] Nevertheless the diagnosis merits consideration in any case of "essential" hypertension and unexplained polyuria in children. Fortunately, simple clinical tests are usually sufficient to evaluate this diagnostic possibility, but the level of aldosterone in the urine should always be determined. Serum potassium and urinary pH determinations are significant screening tests in the study of patients with hypertension or polyuria. Dunstan [18] states that "in patients with long continued hypertension, excretion of alkaline urine with a disproportionate reduction in concentrating power was found to be diagnostic of primary aldosteronism."

The hypertension in the reported patient was very severe, attaining levels of 250 mm. Hg systolic and 140-160 mm. Hg diastolic. During a "cold-pressor" test, the blood pressure reached 280/185 mm. Hg in two minutes after the immersion of the hands in iced water. It is known that patients who have received desoxycorticosterone, or who are fed a very high salt diet, will show an increase in blood pressure as a response to several, normal, neurogenic stimuli. It is interesting that the cold-pressor response in this patient with hyperaldosteronism demonstrated a similar increased vascular reactivity.

Before the true nature of this problem was fully recognized, this patient had been treated with several antihypertensive medications. High doses of hexamethonium (1 gm. daily) resulted in minimal relief of the headaches, and affected the blood pressure very little. Neither reserpine nor hydralazine proved beneficial, but the combination of hydralazine and reserpine lowered the blood pressure appreciably. Daily doses of 1 mg. reserpine (Serpasil) and 300 mg. hydralazine (Apresoline) eliminated the high systolic peaks, although a constant, sustained, diastolic hypertension remained.

The interesting phenomenon produced by the synergistic effect of rauwolfia compounds

and the usual preoperative medications was demonstrated in this patient by severe hypotension occurring prior to anesthesia. The operation was rescheduled two weeks later; the same premedication was again given, but the patient had not received any rauwolfia during the preceding 14 days. No hypotension occurred preceding surgery. There appears to be a synergistic effect on blood pressure between rauwolfia and preoperative medications, notably barbiturates, which merits consideration when planning surgery in patients receiving rauwolfia therapy.

The clinical and pathologic data presented in this report are clear evidence that the described disorder was caused by abnormal function of the hyperplastic adrenal cortex with excess secretion of aldosterone. Inasmuch as severe symptoms had been observed in the third year of life, and the blood pressure was markedly elevated when the patient was only 3 years old, it is considered that this case may represent a form of congenital adrenal hyperplasia or a defect acquired in the second year. Some patients with virilizing congenital adrenal hyperplasia have been shown to excrete increased levels of aldosterone.[19] However, the adrenal disorder in the reported case is very different from that in virilizing adrenal hyperplasia, both clinically and biochemically. In the adrenogenital syndrome, the virilism is associated with marked increases in the excretion of 17-ketosteroids and pregnanetriol, presumably secondary to an enzymatic defect of the cortical cells with deficient biosynthesis of hydrocortisone. In those cases manifesting arterial hypertension as well as virilism, increased levels of the tetrahydro derivative of Compound S (11-desoxycortisone) may also be found in the urine. The reported patient excreted normal quantities of pregnanetriol and tetrahydro S, and only slightly elevated amounts of 17-ketosteroids, and there was apparently no defect in the synthesis of hydrocortisone. In fact, the urinary excretion of unfractionated 17-hydroxycorticoids was significantly above normal for subjects of the same age. These data may indicate a general hypersecretory state of the adrenal cortex, although the most significant biochemical abnormality was the excess of aldosterone. All the clinical features of the disorder can be explained on the basis of the hyperaldosteronism alone.

The response to corticotropin stimulation is of especial interest. It is generally agreed that the secretion of aldosterone is affected to very limited degree by corticotropin stimulation of the adrenal. In this study, small amounts of corticotropin gel were administered in order to measure the sensitivity of the cortex, as well as the nature of its response. As in other recognized types of acquired adrenal hyperplasia, the gland was unusually sensitive to stimulation. In this case, corticotropin administration resulted in a marked increase in the levels of urinary 17-ketosteroids and 17-hydroxycorticoids, as well as a doubling of the excretion of aldosterone. Although the number of determinations does not permit statistical analysis, this result suggests a direct relationship between corticotropin and aldosterone secretion, in accord with the findings of Falbriard.[20] Thus, hyperaldosteronism, which constitutes the third major syndrome related to hyperadrenocorticism, may conceivably be a manifestation of congenital adrenal hyperplasia. Each of the three groups of cortical hormones produces a specific clinical syndrome when secreted in excessive amounts: the corticoids, Cushing's syndrome; the androgens, adrenogenital syndrome; the mineralcorticoids, primary aldosteronism. However, these clinical states do not always appear in "pure" form. Salt-losing types of the adrenogenital syndrome are recognized; various degrees of Cushing's syndrome are known to occur, and finding mixed forms of hyperaldosteronism is not unexpected. Increased levels of aldosterone have already been reported in the adrenogenital[19] and Cushing's syndrome.[21] The ultimate clinical manifestation of the hyperfunctioning adrenal cortex depends on the relative levels of the various hormones produced.

Although there is some evidence that specific histologic "zones" of the adrenal cortex secrete specific hormones,[22] the hyperplasia in the reported case chiefly involved the zona fasciculata, and was indistinguishable from the adrenal glands of many patients with Cushing's syndrome.

Finding normal histology of the kidney was unexpected. The altered renal function was clearly demonstrated by the low urinary sodium, the loss of potassium in the face of marked hypokalemia, marked alkalosis and inability to acidify the urine, hyposthenuria and failure to respond to vasopressin. In many cases this dysfunction is associated with tubular hydropic degeneration, which was not present in the reported case. That the renal dysfunction was actually secondary to the hyperaldosteronism is demonstrated by the reversal of the abnormality following adrenalectomy.

The diagnosis in this patient was established by readily available clinical criteria. The diagnosis was by no means dependent upon the demonstration of increased levels of aldosterone in the urine, but these levels did affirm and support the diagnosis. On the basis of the history and the demonstrated abnormality in water and electrolyte balance alone, but with confirmation by aldosterone levels, adrenal exploration was undertaken. We believe that the best treatment of hyperaldosteronism due to adrenal hyperplasia is total bilateral adrenalectomy. We are aware that subtotal adrenalectomy is a feasible procedure, but the technical aspects of the surgery and the difficulty estimating the quantity of adrenal tissue which, left in place, would secrete the optimum amount of hormone, have led us to favor total adrenalectomy. Furthermore, subtotal removal of hyperplastic glandular tissue leaves the problem of possible recurrent hyperplasia.

Our patient has been maintained with fludrocortisone and cortisone for one year. All symptoms have subsided; his growth and development have progressed normally; there has been no evidence of recurrent disease or complication from therapy.

Summary

The details of a case of primary hyperaldosteronism occurring in a child 10 years of age have been presented. This hyperaldosteronism was proved to be due to bilateral adrenal hyperplasia chiefly involving the zona fasciculata. It is postulated that this hyperplasia was congenital in origin. Hyperaldosteronism should be considered in the differential diagnosis of any case of "essential" hypertension or of unexplained polyuria in children. The determination of serum potassium and urinary pH are useful screening tests in these patients. When hyperaldosteronism is caused by adrenocortical hyperplasia, bilateral total adrenalectomy is recommended. Maintenance of the patient postoperatively with adrenocortical hormones has been completely satisfactory.

NOTE: A new case of hyperplasia in a young adult was reported by B. J. Kennedy et al. at the Endocrine Society, June, 1958.

We are indebted to Dr. Jerome Conn of the University of Michigan for performing the various aldosterone determinations. We also thank Dr. Jacques Genest of the University of Montreal, who analyzed one sample of urine for its content of aldosterone, pregnanetriol, and tetrahydro S.

Henry Ford Hospital (2).

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Abstracts from Current Literature

A. M. A. Archives of Internal Medicine, Chicago
Abstracted by Philip N. Jones, M.D.

102, No. 3 (Sept.) 1958

* Observations on Staphylococcus Albus Septicemia in Mice and Men. I. M. Smith, P. D. Beals, K. R. Kingsbury, and H. F. Hasenclever.—p. 375.
Hemoglobin H Disease. Robert T. S. Jim.—p. 400.
* Second Field Evaluation of Bivalent Types 4 and 7 Adenovirus Vaccine. M. R. Hilleman, J. H. Greenberg, M. S. Warfield, S. A. Anderson, and R. R. Glabere.—p. 426.
* Xanthomatosis and Coronary Heart Disease. J. A. Maher, F. H. Epstein, and E. A. Hand.—p. 437.
Cryptococcosis. A. L. Sciortino, R. A. MacHaffie, G. T. Alliband, and R. L. Zaayer.—p. 450.
Treatment of Tietze Disease with Prednisolone. A. J. McSweeny, T. J. Snodgrass, and P. R. Sholl.—p. 459.
Periodic Neutropenia. George W. Duane.—p. 462.
A Recently Recognized Pathway for Glucose Catabolism—Pentose Phosphate Pathway. Stanley J. Wolfe.—p. 493.

102, No. 4 (Oct.) 1958

* Phenethyl-, Amyl-, and Isoamylbiguanide in the Treatment of Diabetes Mellitus. W. D. Odell, D. C. Tanner, D. F. Steiner, and R. H. Williams.—p. 520.
The Epidemiology of Psittacosis and Report of a Turkey-Borne Outbreak. R. D. Leachman, and E. M. Yow.—p. 537.
Dyschondroplasia and Hemangiomata (Maffucci's Syndrome). H. W. B. Bean.—p. 544.
The Use of Serum Protein Electrophoresis in Clinical Medicine. R. L. Wall.—p. 618.
Evolution of Mitral Valve Surgery. D. M. Hayes.—p. 659.

Observations on Staphylococcus Albus Septicemia in Mice and Men.—The authors present case histories of nine patients suffering from septicemia caused by Staphylococcus albus. They also reviewed the literature concerning this problem. S. albus is generally considered to be nonpathogenic. The authors point out, however, that this can be a very serious problem and if untreated it often is fatal. The disease resembles subacute bacterial endocarditis due to a viridans Streptococcus. Joint pains, chills, and a rash are common and there is frequent involvement of the cardiovascular system at autopsy. It would seem obvious from their report that blood cultures showing S. albus cannot always be dismissed as being due to contamination, and every attempt should be made to do repeat cultures.

Second Field Evaluation of Bivalent Types 4 and 7 Adenovirus Vaccine.—This is an interesting description of the field study performed at Fort Leonard Wood, Missouri, during the winter of 1957. This field study involved 8,238 recruits. Within 30 hours of arrival on the post, each new recruit was given a single 1.5 ml. injection intramuscularly of adenovirus vaccine or of formalin-saline placebo. The personnel in the study were observed during the period from vaccination until completion of their eight weeks' basic training. The evaluation of the vaccine was based on comparison in the vaccinated and placebo control groups of the admissions to the hospital for acute respiratory illness. No data were obtained on any of the recruits who developed respiratory illness but who were not hospitalized. The reduction in the attack rates for the total respiratory disease as the result of vaccination was 55%. The adenovirus specific attack rates calculated on the basis of serodiagnostic tests on approximately half of the patients were 1.6% among the vaccinated group and 16% among the control group. Here the reduction in the attack rate was approximately 90%. These results are rather encouraging, although there are certain limitations to this type of study. It is obvious that many recruits had respiratory infections and either did not report for sick call or were handled strictly as outpatients. Nevertheless it would seem that giving of this vaccine might be of great value among new recruits in the armed forces or among any new arrivals at a large institution. The general use of the vaccine among the general civilian population as a whole does not seem warranted at this time. It must be pointed out in considering use of this vaccine in any population group, that it is important to bear in mind that this adenovirus vaccine is not a common cold vaccine and quite ineffective against the routine common colds which form the bulk of the upper respiratory infections seen in the general population.

* These articles are abstracted in this issue.

Xanthomatosis and Coronary Heart Disease.—The authors present the necropsy findings in two siblings with xanthomatosis who died with coronary arterial disease at the ages of 12 and 16 years respectively. Frequent coexistence of familial xanthomatosis and coronary heart disease has been well established, but there have been relatively few reports of the pathologic findings in such patients. The case report given in this article concerns two teen-age children who died of coronary artery disease. They belong to a family of 18 children. Four of the other children had died suddenly, presumably of xanthomatous heart disease. Of the surviving 12 children, 7 have hypercholesteremia without xanthomatosis and are clinically healthy. Both parents, although hypercholesteremic, are living and healthy. Histochemical studies showed alterations in the ground substance of the arterial walls similar to those seen in patients with atherosclerosis at a later age.

Phenethyl-, Amyl-, and Isoamylbiguanide in the Treatment of Diabetes Mellitus.—The authors present a preliminary report dealing with the oral treatment of diabetic patients with phenethyl-, amyl-, and isoamylbiguanide. All types of diabetes were studied, including juvenile, and all these types have responded. With the materials used there has been no known histologic damage in this study. However, there was a relatively high incidence of side-effects, including anorexia, nausea, vomiting, weight loss, malaise, weakness, and some diarrhea. There was no correlation between age of the patient, duration of the diabetes, and/or previous insulin therapy, and response to the biguanide therapy; but there was an inverse correlation between the dose of insulin necessary to control the diabetes in the percentage of patients responding to the biguanide therapy. It is of interest to note that several cases in which the patient was a severely labile diabetic and could not be controlled on insulin was well controlled on insulin plus the biguanide. It was felt that many mild diabetics were better controlled on the biguanide compound than on insulin alone. This again was true regardless of age, duration of diabetes, or response to tolbutamide. This report was quite encouraging, and this group of drugs is particularly interesting in that they are effective in the juvenile diabetic, whereas drugs such as tolbutamide are not effective in this group of patients. Final evaluation must await a more thorough understanding of its biochemical effects. The high incidence of side-effects seriously limits its use at the present time.

American Journal of Medicine, New York
Abstracted by Hugo Dunlap Smith, M.D.

25, No. 3 (Sept.) 1958

° Subacute Hepatic Necrosis and Postnecrotic Cirrhosis Due to Anicteric Infections with the Hepatitis Virus. Gerald Klatskin.—p. 333.

Peroral Small Bowel Mucosal Biopsy. Robert B. W. Smith, Helmuth Sprinz, William H. Crosby, and B. H. Sullivan Jr.—p. 391.

Clinical Diagnosis of Systemic Lupus Erythematosus. R. Armas-Cruz, J. Harnecker, G. Ducach, J. Jalil, and F. Gonzales.—p. 409.

° Haemodialysis in Acute Acetylsalicylic Acid Poisoning. A. C. Thomsen and O. Z. Dalgard.—p. 484.

25, No. 4 (Oct.) 1958

Observations on the Pathogenesis of Renal Tubular Acidosis. Telfer B. Reynolds.—p. 503.

Anuria Complicating the Treatment of Leukemia. Robert A. Kritzler.—p. 532.

Circumstances Surrounding Complications of Cerebral Angiography: Analysis of 546 Consecutive Cerebral Angiograms. David R. Coddon and Howard P. Krieger.—p. 580.

Diagnostic Significance of the Muscle Biopsy. Stanley L. Wallace, Raffaele Lattes, and Charles Ragan.—p. 600.

° Simultaneous Placental Transfer of Factors Responsible for L. E. Cell Formation and Thrombocytopenia. Daniel J. Nathan and I. Snapper.—p. 647.

25, No. 5 (Nov.) 1958

° Transitory Congenital Neutropenia: A New Syndrome: Report of Two Cases. Mario Stefanini, Rose H. Mele, and David Skinner.—p. 749.

Subacute Hepatic Necrosis and Postnecrotic Cirrhosis Due to Anicteric Infections with the Hepatitis Virus.—Postnecrotic cirrhosis represents approximately 10% of all adult cirrhosis. Although a clear-cut etiology can be demonstrated in only a minority of cases of postnecrotic cirrhosis, the hepatitis virus is thought to be a common precursor. Of 69 cases of postnecrotic cirrhosis studied at the New Haven Hospital, 53 were of presumed viral etiology. Klatskin analyzed the findings in nine patients in whom the antecedent illness was without icterus but otherwise was, retrospectively suggestive of viral hepatitis. Two to eighteen months after their original illness, frank signs of liver involvement occurred

with jaundice, mild hepatomegaly, and weight loss being prominent. In the later stages, mild splenomegaly, esophageal varices, positive flocculation tests, hyperglobulinemia, and hypoalbuminemia were common. Dark urine, light stools, and elevation of the alkaline phosphatase falsely suggested biliary obstruction in about half the patients.

The disease tended to run an intermittently progressive and downhill course that was little affected by dietary measures and bedrest. It was felt that prolonged steroid therapy might be effective.

Liver biopsies early in the illness demonstrated both the histologic features usually considered diagnostic of viral hepatitis and the changes of subacute hepatic necrosis. Subsequent biopsies manifested progression to post-necrotic cirrhosis. Klatskin concludes that these changes represent post-necrotic cirrhosis following anicteric viral hepatitis.

Comment: Although the cases reported by Klatskin involved adults and especially older women, and, despite the fact that viral hepatitis seems less commonly to cause permanent liver damage in children than in adults, occasional children are seen with apparent subacute hepatic necrosis. This may follow both icteric and nonicteric illnesses and at times is seen to progress to cirrhosis and death.

Haemodialysis in Acute Acetylsalicylic Acid Poisoning.—Thomsen and Dalgård report a case of suicidal ingestion of 150 gm. of acetylsalicylic acid by an adult. In addition to the common manifestations of central nervous system stimulation and of gastrointestinal irritation, the patient developed shock and subsequent renal insufficiency. Dialysis with the artificial kidney was therefore performed, with dramatic relief of the hyperpnea, restlessness, and confused sensorium. During the five and a half hour period of dialysis, the serum salicylic acid level fell from 51.0 to 24.8 mg. per 100 ml. and the serum urea from 264 to 64. Subsequently renal function was restored, and the patient recovered.

A review of other reports indicates successful removal of up to 10 gm. of salicylic acid by dialysis in adults, with dramatic declines in serum salicylate levels. This fact would indicate that although 50%-80% of the salicylate in human plasma is bound to plasma protein; the bond is loose. Also the small amounts of salicylic acid removed by dialysis compared with the amounts ingested would indicate that the greater part of the ingested dose may escape absorption as a result of vomiting and diarrhea.

Comment: For occasions of severe salicylate intoxication, dialysis by an artificial kidney may be life-saving for children as well as adults. If an artificial kidney is not available, exchange transfusion may be used. In Cincinnati the use of the artificial kidney or of exchange transfusion is considered in all children with salicylate levels over 60 mg. % and in those with markedly diminished ability to excrete salicylate by the kidney.

Simultaneous Placental Transfer of Factors Responsible for L. E. Cell Formation and Thrombocytopenia.—Nathan and Snapper report the case of a young woman with systemic lupus erythematosus (S. L. E.) who, two days after giving birth to a premature infant, was found to have thrombocytopenia with circulating anti-platelet antibodies. The infant, although apparently normal physically, manifested a mild positive L. E. preparation on the second day of life but not thereafter and was found to have thrombocytopenia with antiplatelet antibodies. These platelet abnormalities had disappeared by the third week of life.

In discussing this case the authors review much present-day knowledge about certain platelet disorders. Neonatal thrombocytopenia may be "primary" and due to fetal-maternal platelet incompatibility (similar to erythroblastosis with red blood cell incompatibility), or "secondary" and consequent to maternal thrombocytopenia—past or present—with transplacental transfer of maternal platelet antibodies. Outside of the neonatal period, antiplatelet antibodies are commonly present in idiopathic thrombocytopenia and hypersplenism, and usually absent in disorders such as leukemia which cause decreased platelet production. Steroid therapy may be of value in those disorders associated with platelet antibodies.

Although the thrombocytopenia seen in S. L. E. is thought to be usually due to hypersplenism, it rarely is associated with platelet antibodies. Pregnancy in women afflicted by S. L. E. does not increase the severity of the mother's illness, has little or no influence on the viability or normality of the fetus, and is not associated with manifestations of S. L. E. in the infant. Only rarely has serum from the infant manifested the L. E. phenomena and then only transiently. Present thought is that the L. E. factor which resides in the gamma globulin fraction of blood represents an anticell nucleus antibody.

Transitory Congenital Neutropenia: A New Syndrome; Report of Two Cases.—Stefanini, Mele, and Skinner report on the occurrence of a transient congenital neutropenia in two babies born of mothers with severe prolonged neutropenia. Immunologic studies revealed the presence of a neutropenic factor in the serum of one mother and her baby but not of the other mother and baby. The titer of this factor in the first baby's serum declined steadily from birth until it no longer could be found by the 15th day of life. In vitro the factor was shown to cause agglutination and lysis of normal white blood cells, whereas in vivo it depressed the neutrophil count and caused a transient bone marrow picture of granulocytic hyperplasia with maturation arrest in normal persons receiving serum from these patients. These same bone marrow changes were observed in both babies during the first three days of life, while marrow specimens obtained one month later were normal. Although the neutropenia was transient in the infants, it persisted in the mothers, being associated with hyperplasia of the gums and with frequent infections. Therapy with folic acid, ACTH, adrenal cortical steroids, and pyridoxine was without benefit. Splenectomy, while resulting only in transient increases in the neutrophil count, was followed by a decrease in the incidence of infections. Another baby was born to one of the mothers after splenectomy, and this baby also had a transient neutropenia. Splenectomy did not result in a decline in the titer of the neutropenic factor in the serum of the mother having such a factor.

This report would indicate that transient congenital neutropenia may occur consequent to the transplacental transfer of a neutropenic substance from the serum of mothers with neutropenia. This would appear to be an immunologic neutropenia. Other causes for congenital and neonatal neutropenia are briefly reviewed.

American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Springfield, Ill.

Abstracted by Donald H. Altman, M.D.

80, No. 3 (Sept.) 1958

* Ultra-Short (Millisecond) Timing in Roentgen Diagnostic Procedures Including Angiocardiography: Comparison of Dynapulse and Impulse Timing. Barton R. Young, Robert B. Funch, Jay W. MacMoran, Herbert M. Stauffer, and Morton J. Oppenheimer.—p. 375.

* Angiocardiographic Features of the Bland-White Syndrome. Erich K. Lang, Leon A. Phillips, and John G. McAfee.—p. 381.

Reaction of the Heart to Selective Angiocardiography. Russell A. McFall, Andrew H. Dowdy, and Bernard J. O'Loughling.—p. 394.

* Cor Triatrium Sinistrum. C. H. (Joseph) Chang and James V. Rogers.—p. 407.

The Relationship of Systemic Venous Anomalies to the Paravertebral Veins. Herbert L. Abrams.—p. 414.

Congenital Hypertrophic Emphysema. Longstreet C. Hamilton and Robert W. Gillespie.—421.

Roentgenographic Demonstration of a Duodenal Ulcer in the Neonatal Period. A. J. Barger.—p. 426.

* The Significance of Subdural Air in Pneumoencephalograms in Infants. Robert P. Boudreau and R. M. N. Crosby.—p. 429.

Roentgenographic Depictions of Cerebral Ependymomas in Children. Edgar F. Fincher.—p. 436.

Calcification of the Hyoid, Thyroid and Tracheal Cartilages in Infancy: Report of a Case. P. E. Russo and C. G. Coin.—p. 440.

Chondrodystrophia Calcificans Congenita. Byron G. Brogdon and Neil E. Crow.—p. 443.

* Achondroplasia of Pelvis and Lumbosacral Spine: Some Roentgenographic Features. John Caffey.—p. 449.

* Pelvic Bones in Infantile Mongoloidism: Roentgenographic Features. John Caffey and Steven Ross.—p. 458.

Severe Idiopathic Hypercalcemia of Infancy. S. B. Feinberg and A. R. Margulis.—p. 468.

Agammaglobulinemia: A Case Report and Discussion. Joseph H. Allen Jr.—p. 475.

Maffucci's Syndrome: Dyschondroplasia with Hemangiomatosis; Report of a Case. S. L. Beranbaum and G. Tzamouranis.—p. 479.

Roentgenographic Appraisals of Skeletal Growth and Development: Reliability and Influencing Factors. Harriet J. Kelley and Icie G. Macy.—p. 482.

Juvenile Unicameral Bone Cyst: A Roentgen Reappraisal. Gwilym S. Lodwick.—p. 495.

Radiation Therapy of Solitary Benign Cystic-Appearing Lesions Involving the Long Bones of Children. James C. Cook, Kenneth L. Krabbenhoft, and Robert Songe.—p. 505.

80, No. 4 (Oct.) 1958

* A Classification of the Urographic Patterns in Children with Congenital Bladder Neck Obstruction. Aurelio C. Uson, Donald W. Johnson, John K. Lattimer, and Meyer M. Melicow.—p. 590.

* The Intravenous Urogram in Acute Leukemia. Lee B. Lusted, Byron E. Besse Jr., and Richard Fritz.—p. 608.

An Evaluation of the Somatic and Genetic Hazards of the Medical Uses of Radiation. Henry S. Kaplan.—p. 696.

80, No. 6 (Dec.) 1958

* Roentgenographic Study of Congenital Choledochal Cysts: Pre- and Postoperative Analysis of Five Cases. Edwin J. Liebner—p. 950.

An Automatic Injector for Angiography. Fred C. Shipps.—p. 982.

Ultra-Short (Millisecond) Timing in Roentgen Diagnostic Procedures Including Angiocardiography: Comparison of Dynapulse and Impulse Timing.—This article evaluates a new electronic switching system capable of roentgenographic exposures at 1/1,000 second with those of a reliable impulse timer of 1/120 second. The photographically effective portion of the impulse-timed exposure is about 1/200 second, thus making the dynapulse five times as fast.

Mechanical testing revealed motion of 80 cm. per second which is "stopped" by a millisecond exposure compared with 20 cm. per second by 1/120 second. This finding may be of importance in angiocardiographic procedures since maximal rate of flow in man is estimated to approach 100 cm. per second.

Chest roentgenograms of children made with a dynapulse timer at 1/1,000 second revealed no improvement over films made with impulse timer at 1/120 or 1/60 second, as both methods eliminated motion due to pulsation of the pulmonary vessels.

Venous angiograms on dogs at 1/120 and 1/1,000 second were of excellent quality and there was no appreciable difference in sharpness. Left-sided angiograms following injection of opaque contrast material into the left ventricle showed no appreciable difference between the two methods.

Millisecond timing did reveal an advantage in stopping motion of particulate oil contrast material injected into the left ventricle of dogs via a catheter. This has little practical value, as particulate contrast material is not used in humans in this manner.

No advantage was observed in cerebral angiography.

Angiocardiographic Features of the Bland-White-Garland Syndrome.—Anomalous origin of the left coronary artery from the pulmonary artery is recognized with increasing frequency. In 1933 Bland-White-Garland described characteristic electrocardiographic changes and clinical features.

The article presents four cases with characteristic angiocardiographic findings. The findings in 66 cases of anomalous origin of the coronary arteries are summarized.

Clinical History.—The children appear normal at birth and are asymptomatic for the first few weeks of life. Feeding difficulties tend to ensue in the second month. These are probably manifestations of angina pectoris. Transient or circumoral cyanosis is common.

Clinical Manifestations.—The commonest form involves the left coronary artery and presents clinically in infancy.

Murmurs are usually absent. Sudden death is common and the majority die between the ages of 2½ and 13 months.

In the asymptomatic neonatal phase the high pulmonary pressure and patent ductus arteriosus help to maintain a reasonably adequate coronary flow. Later, however, the fall in pulmonary artery pressure and the increasing work load of the left ventricle result in anoxia and myocardial damage. The secondary stasis further decreases the pulmonary and left coronary artery flow, and a vicious cycle is established.

An acute anterolateral infarction pattern at this age is almost pathognomonic.

Pathology.—The aberrant left coronary artery usually arises from the pulmonary artery above the lateral pulmonic cusp.

A possible theory for origin of this anomaly is that the aorticopulmonary septum may be malrotated so that the ostium of one coronary artery is included in the pulmonary side rather than the aortic side of the septum. The left ventricular chamber is hypertrophied at the ventricular septum, base, and posterior wall of the left ventricle.

X-Ray Manifestations.—Cardiac enlargement, left ventricular preponderance, normal or slightly increased pulmonary vascularity. Atelectasis of the left lower lobe is common, probably due to enlargement of the left ventricle compressing the left lower lobe bronchus.

Angiocardiographic Manifestations.—The right chambers are usually normal, but the right ventricle may be displaced to the right owing to a grossly enlarged left ventricle, and they are rendered concave by the bulging ventricular septum.

The left ventricle remains opacified for a prolonged period because of its huge size and because of slow circulation time. The hypertrophied wall of the left ventricle is seen at the base of the heart in the A. P. view and at the ventricular septum in the lateral view, whereas in contrast there is marked thinning at the apex.

This serves as a differential diagnostic point from subacute endocardial fibroelastosis, congenital aortic or subaortic stenosis, Fiedler's idiopathic myocarditis, or von Gierke's disease, where the apex is thickened.

Cor Triatriatum Sinistrum.—This is a rare congenital anomaly in which a fibromuscular septum divides the left atrium into two chambers. The septum separates the opening of the pulmonary veins from the mitral orifice.

Twenty-eight cases have been reported since the original description in 1829. The first case during life was described in 1957 (Barrett and Hickie).

The circulatory effect is physiologically similar to that observed in mitral stenosis.

Longevity depends upon the size and completeness of the anomalous septum, the size and number of perforations in the septum, the presence and size of a patent foramen ovale, and the presence and severity of other associated defects.

Most patients die during infancy and in the first four months of life.

The most accepted embryologic explanation is that this represents a failure of the common pulmonary vein to be incorporated into the left atrium.

A case is presented in which the diagnosis was made at autopsy.

The x-ray findings are not characteristic, but a prominent pulmonary artery segment is present in almost all cases. The lung fields are usually congested.

Clinically, respiratory embarrassment secondary to congestion with subsequent right ventricular failure is the prominent feature of all cases with symptoms.

The ECG recorded in all the cases where it has been done has always revealed right ventricular hypertrophy.

The diagnosis of this condition in infancy is to be differentiated from other conditions causing cardiac enlargement and cardiac failure, especially when there is obscure pulmonary hypertension.

The Significance of Subdural Air in Pneumoencephalograms in Infants.—The material at the University of Maryland Hospital was reviewed with the aim of determining if the presence of subdural air in the pneumoencephalogram can contribute in any way to the diagnosis of subdural effusions.

One hundred fifty-nine pneumoencephalograms made during a four-year period on infants under 2 years of age were reviewed. Of these, 66% or 41% showed the presence of subdural air in some form. In order to demonstrate subdural air collections erect horizontal beam roentgenograms are made routinely. Such collections were found to have pathognomonic significance as regards subdural effusions only when they had a certain configuration and fulfilled certain criteria:

Group I—Subdural air overlying the cerebral hemispheres in such a way that the dura was clearly separated from the arachnoid

Group II—A subdural air collection overlying the cerebral hemispheres which was small in amount and did not move freely

Group III—Subdural air merely outlining the tentorium or falx.

In most cases falling into Group I, 94% (33 of 35 cases) had subdural effusion. Eighteen, or 54%, of these cases had bilateral subdural air collections; thus this finding is strong corroborative evidence of subdural effusion.

Those falling into Group II had subdural collections of fluid in only 6 of 17 cases, but this serves as an indication for subdural taps or trephination in the author's opinion.

The findings in Group III were not significantly correlative.

Achondroplasia of Pelvis and Lumbosacral Spine: Some Roentgenographic Features.—The findings in the flat and short bones of the pelvis and lumbosacral spine in achondroplasia have not been adequately described heretofore, according to the author.

Primary causal mechanisms in achondroplasia are slowed cartilaginous growth and irregular enchondral bone formation in all bones of cartilaginous origin.

All parts of the bony pelvis are smaller in achondroplasts at all ages. Pelvic diameters are shortened more in length than in breadth. Iliums are much more dwarfted than ischiums and pubic bones.

Acetabular angles are reduced to nearly zero. Cartilage is excessive and is indicated by increased cartilage spaces and reduction of cartilage centers.

In the newborn and the prenatals the greater sciatic notches are reduced to narrow deep clefts, and in the achondroplastic spines the intervertebral spaces are considerably thicker than their contiguous vertebral bodies.

Dorsal edges of vertebral bodies are convex. Undergrowth of pedicles is a conspicuous feature of achondroplastic vertebras.

Regional undergrowth of the ventral ends of some lumbar bodies appears to be responsible for their wedging ventrad. The fourth and fifth lumbar segments are most affected.

Pelvic Bones in Infantile Mongoloidism: Roentgenographic Features.—The diagnostic changes in the pelvic bones of infants were first described by Caffey et al. in 1956, and the two cardinal diagnostic features were (1) flattening of the under edges of the ilium measured quantitatively at the acetabular angle, and (2) widening of the iliac wings and bodies, measured at the iliac angles.

These measurements were greatly reduced in Mongoloid infants, and an iliac index, representing the arithmetic sum of these two angles, also was significantly smaller than the iliac indices for normal infants.

The scores for 29 of 36 Mongoloid hips lay at or beyond the lower limits of the normal two standard deviation zones.

The present study is of 48 Mongoloid infants who varied in age from 2 days to 12 months.

In this group there were no significant differences between Mongoloid boys and girls, denying the earlier impression that pelvic changes were more marked in boys. It is also evident in this study that bilateral smallness in the girth of the ischial rami, both superior and inferior, is a common and an important diagnostic change. Bilateral coxa valga is a persistent finding. The smallness of the ischial rami and coxa valga deformities may both represent hypoplasia and deformity of disuse in mongoloid infants who have weak hypotonic pelvic and thigh musculature.

The roentgenographic findings in the pelvis are clearly diagnostic in about 4 out of 5 Mongoloids, suggestive in about 4 of 20, and uncertain or normal in less than 1 out of 20. The complete complex of the typical case (three out of four), bilateral flat acetabular angles, bilateral widened iliums, bilateral slender ischial rami, and bilateral coxa valga, is not seen in normals or in any other disease, although single elements of the complex are found in normals and in some diseases.

The Intravenous Urogram in Acute Leukemia.—Although kidney enlargement in acute leukemia is usually attributed to infiltration with leukemic cells, the authors state that renal enlargement is common in patients dying with acute leukemia and is not necessarily caused by leukemic cell infiltration.

This article deals with the renal findings in 85 patients with acute leukemia—41 children and 44 adults.

Roentgenographic Findings.—All of the intravenous urograms showed that the calyces and infundibula were elongated without real deformity. The renal pelves were enlarged without evidence of obstruction. Some decrease in function was noted in kidneys with and without leukemic infiltration.

The authors conclude that intravenous urography does not help to differentiate the kidney enlargement caused by leukemic cell infiltration from the enlargement caused predominantly by edema or hemorrhage.

A Classification of the Urographic Patterns in Children with Congenital Bladder Neck Obstruction.—One hundred thirty-three cases of congenital bladder neck obstruction are presented and discussed. The cases are divided as follows:

Group I. No vesico-ureteral reflux is demonstrated by cystography.

Type A (13 cases). The upper urinary tracts are normal.

Type B (8 cases). There is unilateral hydroureteronephrosis of variable degree with trapping of urine in the dilated ureter.

Type C (23 cases). There is bilateral hydroureteronephrosis, usually with impairment of renal function and obstruction at the ureterovesical junction.

In these types the bladder is large and ovoid and the bladder wall may be smooth or trabeculated. In Types "B" and "C" a juxtameatal vesical diverticulum may be seen.

Group II (89 cases). Vesicoureteral reflux is revealed by cystography.

Type A (11 cases). There is unilateral vesicoureteral reflux with a variable degree of hydroureteronephrosis. An organic obstruction at the ureterovesical junction is not always present.

Type B (20 cases). There is dilatation of both upper urinary tracts with vesicoureteral reflux on one side and ureterovesical obstruction on the opposite side.

Type C (58 cases). Bilateral vesicoureteral reflux with bilateral hydroureteronephrosis. Postvoiding cystograms show residual urine in the bladder because of the bladder neck obstruction and also in the upper tracts because of ureteral redundancy, atony, and at times strictures at the ureterovesical junctions.

An excellent diagrammatic representation of the various types of lesions is presented and shows the situation in each, the filled, delayed, and postvoiding cystograms, and in the intravenous pyelogram.

Retrograde ureterography is seldom used, and the hazard of this procedure is stressed.

Only 12 cases of posterior urethral valves were found in 158 cases of bladder neck obstruction. In 4 of the 12 cases with urethral valves congenital deficiency of the abdominal musculature was also present.

The cause, development, and significance of the juxtameatal diverticula, which were encountered in some of these patients, are not fully understood. The authors believe the diverticula are of congenital origin.

Roentgenographic Study of Congenital Choledochal Cysts: Pre- and Postoperative Analysis of Five Cases.—Correct preoperative diagnosis of congenital choledochal cysts has seldom been made prior to the use of intravenous opaque media.

The entity occurs four times as frequently in females as in males. This article presents findings in four children and one adult.

The clinical features include: abdominal pain, 60%; tumor mass, 80%, and jaundice, 70%. The triad is present in 60% of the cases. The over-all mortality average is 58% to 69%. However, with primary anastomosis of the biliary and intestinal tract the mortality is reduced to 9%.

The five patients discussed all had a Roux en Y anastomosis.

Radiographically the diagnosis is suspected by the finding of a right upper quadrant mass displacing adjacent structures. The oral cholecystogram is usually of no aid. Nonvisualization is a frequent finding. The intravenous cholangiogram is diagnostic if the serum bilirubin levels are within normal ranges.

Blood, New York

Abstracted by Audrey K. Brown, M.D.

13, No. 7 (July) 1958

* Editorial: On the Specificity and Reactivity of Coombs' Antiglobulin Sera. S. Haberman.—p. 688.
Paroxysmal Nocturnal Hemoglobinuria: The Role of Properdin in the Diagnostic Thrombin Test. W. H. Crosby and N. R. Benjamin.—p. 684.

13, No. 8 (Aug.) 1958

* Hereditary Methemoglobinemia in Alaskan Eskimos and Indians. E. M. Scott and D. D. Hoskins.—p. 795.
Clinical Evaluation of 6-Chloropurine in Leukemia of Adults. R. R. Ellison.—p. 705.
Inhibition of Leukocyte Agglutination by Serum from Patients with Systemic Lupus Erythematosus: A Manifestation of the L. E. Cell Phenomenon. S. L. Lee.—p. 778.
Survival Studies of Thalassemic Erythrocytes Transfused into Donors, into Subjects with Thalassemia Minor and into Normal and Splenectomized Subjects. C. Vullo and A. M. Tunioli.—p. 803.

Editorial: On the Specificity and Reactivity of Coombs' Antiglobulin Sera.—This editorial points out that commercial producers of Coombs' antiglobulin sera employ a variety of methods and animals in the production of this reagent. Because of this the author has compared the reactions of different sera on normal and antibody-coated erythrocytes from newborn children including those with erythroblastosis due to ABO or Rh-Hr systems as well as other hemolytic anemias. Further a two-year survey of mothers and infants was made. The maternal sera were studied using the indirect Coombs' test with a panel of selected erythrocytes containing known antigens. The infants' erythrocytes were tested by the direct Coombs' technique.

The variations in specificity and sensitivity of the six antisera used indicated that the various Coombs' antiglobulin sera might not give equivalent results. Some failed to detect ABO isoimmunizations. The author lists as factors leading to such differences the lack of some of the desired human globulins in the antigens used to stimulate the production of Coombs' reagents or the failure of the animals used to produce the desirable antiglobulin of the agglutinating variety.

When Coombs' antiglobulin serum was standardized against immune antibodies of the ABO and other systems, as well as those of the Rh-Hr group, improved laboratory demonstration of

the isoimmunization of pregnancy in mothers and infants of incompatible blood group pregnancies resulted.

It seems desirable to have reference standards for Coombs' testing sera. Until that time, reliance should not be placed on reaction obtained with a single antiglobulin serum.

Hereditary Methemoglobinemia in Alaskan Eskimos and Indians.—Hereditary methemoglobinemia is a very rare condition characterized by cyanosis, a variable amount of hemoglobin in the oxidized form methemoglobin, a compensatory polycythemia, and no other pathologic changes. The authors describe an unusually frequent occurrence of this disorder in Alaskan Eskimos and Indians. Fifteen cases in a population of about 20,000 are known. The rate of reduction of methemoglobin by red cells and hemolysates was below normal in the three cases in which this was tested. This finding as well as others suggested that these cases of methemoglobinemia was not due to hemoglobin M.

It is interesting that all of the cases described by the authors were children. In one case there seemed to be a decrease in methemoglobin with age.

The amount of methemoglobin in a given patient was variable and seemed dependent upon some environmental influence such as dietary intake of ascorbic acid.

Boletín médico del Hospital infantil, México, D. F.

Abstracted by Mary Allen, M.D.

15, No. 5 (Oct.) 1958

Clinical Appraisal of Benign Infectious Hepatitis in Hospital Infantil. Jesus Kumato, Lozaro Benavides, and Julio Carrillo.—p. 595.

* Acute Vascular Purpura and Its Renal Lesion. Raphael Soto, Gustavo Gordillo, Francisco Uribe, and Pedro Gonzalez.—p. 619.

Some Clinical Observations Regarding 46 Cases of Amebiasis in Children. Francisco Biagi.—p. 633.

Poisoning in Children (Analysis of Cases Seen in Emergency Service). Jesus Gomez Orozco.—p. 639.

Cystic Lymphangioma of the Neck. Jose Luis Delgado and Eugenio Esparza.—p. 657.

Skin Diseases in Children. Luis Gomez Orozco and Fernando Rojas Villezas.—p. 665.

Recovery of a Case of Hepatic Coma Following Hepatitis. Jesus Kumate, Alfredo Heredia, Alfanzo Juarez, and Jose Trevino Alonzo.—p. 683.

Epidemic Typhus: Study of Three Clinical Cases. Dr. Pagola.—p. 697.

Anuria Due to Upper Ureteral Obstruction. Rafael Soto, Gustavo Gordillo, Carmen Gil Mota, Francisco Uribe, and Jose de J. Casteneda.—p. 703.

15, No. 6 (Dec.) 1958

Malnutrition in Children. Ramos Galvan and J. Cravioto.—p. 763.

Metabolism of Water and Electrolyte in Preschool Children with Chronic Malnutrition. Silvester Frenk.—p. 789.

Certain Aspects of Fat Metabolism in Chronic Malnutrition of Children. J. Cravioto.—p. 805.

Some Aspects of Fat Metabolism in Chronic Malnutrition of Children. J. Cravioto.—p. 823.

Operation Zacatepec: Part III. The Evaluation of One State of Nutrition in the Children of a Rural Community. Rapheal Ramos-Galvan, Joaquin Cravioto, Gonzalo Gutierrez, Federico Gomez, and Silvester Frenk.—p. 855.

* Mortality in the Malnourished Child. Raphael Ramos-Galvan, Joaquin Cravioto, and Arturo Navarrete.—p. 875.

Epidemiological Considerations and a Basis for a Program for Prevention of Malnutrition. Joaquin Cravioto.—p. 925.

Treatment of Malnutrition with Special Reference to Third Degree Malnutrition. Raphael Ramos-Galvan.—p. 941.

The Syndrome of Nutritional Recuperation in Children with Chronic Malnutrition. Raphael Ramos-Galvan and Humberto Garcia Alonso.—p. 965.

Acute Vascular Purpura and Its Renal Lesion.—The authors review the literature on acute vascular purpura, also called anaphylactoid purpura and Shoenlein-Henoch's syndrome. They review cases (55) of acute vascular purpura in the Children's Hospital of Mexico City during 1953-1956. The development and clinical course of 23 cases were followed during four years. They analyzed the case under three headings: (1) clinical manifestations; (2) laboratory findings; (3) sequelae.

The clinical manifestations included a study of previous history of allergies and infections, purpuras, abdominal and joint pains, nausea and vomiting, hematemesis and melena, macroscopic hemituria, hypertension and edema and inflammation of joints.

Laboratory data compiled were blood studies, urinalysis, blood urea, blood and throat cultures.

The prognosis was analyzed (1) under number of recurrent illnesses, (2) total time of illness, (3) duration of the nephritic symptoms, and (4) condition on discharge from the hospi-

tal. It is the belief of authors that the renal involvement is frequently overlooked in acute vascular purpura; frequently nephritis is overlooked and not noted until glomerulonephritis occurs later and is said to be a chronic nephritis without previous infection. The glomerulonephritis may be mild during the purpura attacks, or it may develop only after the recovery of the purpuric symptoms. In their group of patients 12% had chronic glomerulonephritis. Others had only mild renal involvement. There was one death.

Beta hemolytic Streptococcus seems to be a very important factor and should be considered a concomitant disease much in the same way it is in rheumatic fever.

Since there is no specific treatment, it is very important to evaluate the therapeutic procedures to be followed in these cases. The indiscriminate use of antibiotics, steroids, and other drugs may cause much damage unless they are individually prescribed.

Mortality in the Malnourished Child.—The authors analyze meticulously the clinical histories of 1,100 children admitted to the Nutrition Service of the hospital from 1953 to 1957 inclusive.

There are many figures given of many categories and percentages as well as calculations regarding statistical signficance. Since the entire issue is on nutritional problems, many of the ideas and philosophy are repeated in this article.

The suspicion, which has been sustained in very few studies, that the younger the child the higher the mortality is proved statistically in this group. The mortality falls directly with increased age up to the eighth year. The differences in mortality rate between the first and second year in cases of severe malnutrition were not statistically significant, but they were quite significant between the first and third year, and between the second and fourth year.

In a more detailed study the differences in infants with electrolytic imbalance and those without, are studied.

In studies of patients with different degrees of malnutrition, no correlation with age could be established in the first two degrees of malnutrition since most of the material in the study was among children with severe malnutrition with weight loss of 54% ±12 for all ages.

However, it was possible to demonstrate the lack of any "clinical type" of malnutrition with regard to death rate in older children. Whether the children showed signs of edema, the skin lesions typical of Kwashiorkor marasmus, or marasmus alone, the mortality rate was about the same, having no statistical significance.

In marasmus, however, the rate in the first year of life was 43% and it fell to 32% in the second year of life.

Certain symptoms classified as universal signs of malnutrition such as blood studies, serial albumin values, and chronicity as measured by bone age were not significant in the mortality rates.

Conditions concomitant with malnutrition which were of significance in prognosis of mortality were in descending order: (1) electrolytic imbalance, (2) bronchopneumonia and similar infections, (3) diarrheas, (4) age, and (5) severity of malnutrition.

The study revealed the appearance of some new signs which are viewed as of interest with regard to prognosis. Leukopenia and neutropenia in the presence of infection was a serious sign; hypothermia and purpura were very significant findings statistically relevant with regard to the mortality rate.

Journal of Clinical Endocrinology and Metabolism, Springfield, Ill.

Abstracted by Judson J. Van Wyk, M.D.

18, No. 8 (Aug.) 1958

Action of Glucagon-Insulin Mixtures in Diabetic Patients. H. Elrick, Y. Arai, and C. J. Hlad Jr.—p. 825.

Interstitial-Cell Tumor of the Testis with Gynecomastia. W. L. Herrmann, F. Buckner, and A. Baskin.—p. 834.

* Effect of Oral and I. V. Cobaltous Chloride on Thyroid Function. K. R. Paley, E. S. Sobel, and R. S. Yalow.—p. 850.

Amelioration of Hypercalciuria Following Poliomyelitis by 17-Ethyl, 19-Nortestosterone (Nilevar). F. Plum and M. F. Dunning.—p. 860.

Serum Transaminase Activity in Uncomplicated and Complicated Pregnancy and in Newborns. N. E. Borglin.—p. 872.

Serum Transaminase Activity and Vitamin B_6 in Pregnancy. N. E. Borglin.—p. 878.

Changes in Plasma Level of 17-OHCS Induced by ACTH: III. Effects of Various Vehicles and Modes of Administration. E. Eik-Nes, A. A. Sandberg, F. H. Tyler, and L. T. Samuels.—p. 882.

* Juvenile Hypothyroidism with Precocious Sexual Development. H. K. Silver.—p. 886.

Clinical and Microscopic Findings in Gonadal Dysgenesis. D. R. Eppa, M. F. M. Guerios, A. da S. Coelho Neto,

N. Leon, L. M. De Assis, and A. B. de Ulhoa Cintra.—p. 892.
* Treatment of a Pituitary Dwarf with Human Growth Hormone. M. S. Raben.—p. 901.
The in Vivo Conversion of Thyroxine to 3:5:3'-Triiodothyronine. W. E. Lassiter and J. B. Stanbury.—p. 903.
Alterations of Adrenal Steroid Patterns in Man Resulting from Treatment with a Chemical Inhibitor of 11 Beta-Hydroxylation. G. W. Liddle, D. Island, E. M. Lance, and A. P. Harris.—p. 906.

Treatment of a Pituitary Dwarf with Human Growth Hormone.—Growth hormone was obtained from human pituitary tissue obtained at autopsy and administered to a 17-year-old male hypopituitary dwarf for a period of 10 months. The dosage of 1 mg. twice a week produced an initial stimulation of growth, but this growth was not maintained. Two mg. two times a week was effective for at least seven months of the treatment period, producing a growth rate of 2.6 in. a year as compared with 0.5 in. per year during the one and a half year period before treatment. The total increase in height during the 10 months of growth hormone therapy was 2.1 in., representing a growth rate slightly greater than that of a normal child of the same height. The concentration of inorganic phosphorus in the serum increased from 3.6 mg. to 6.0 mg. per 100 ml. during treatment, and alkaline phosphatase activity rose from 4.2 to 6.0 Bodansky units. There was no advance in bone age during the period of growth hormone therapy. The therapy was well tolerated and no other trophic hormone effects could be demonstrated. No diabetogenic effect was encountered.

Comments: For many years purified growth hormone has been available from pigs, sheep, and cattle. All of these preparations not only have been inactive in the human, but actually produced a negative nitrogen balance. These preparations were likewise ineffective in the monkey. With the availability of large numbers of monkey pituitaries from animals used in the preparation of Salk vaccine, a preparation of growth hormone was obtained from primate sources, which was active in the human. It was soon discovered that the human postmortem pituitary is a rich source of growth hormone, and limited amounts have become available for clinical investigation. Although acute balance studies have demonstrated the potency of this preparation as judged from its effect on nitrogen balance, the present report is the first long-term study to appear in print. The present study confirms that a true growth-stimulating effect results from growth hormones without an accompanying disproportionate increase in skeletal maturation. Growth hormone is unique in this property. In the substitution dosages employed in this study the absence of hyperglycemia is encouraging. Further studies should be forthcoming as larger supplies become available.

Effect of Oral and Intravenous Cobaltous Chloride on Thyroid Function.—Following oral administration of cobaltous chloride (37.5 mg. of cobalt per day) for more than 10 days, there was marked depression of thyroidal I^{131} uptake at half an hour and at 24 hours, in two of four patients. In one of these subjects, half an hour after administration of I^{131}, thyroidal radioactivity was discharged almost completely by 1.0 gm. of NaSCN intravenously. In one of two subjects who received both oral and supplemental intravenous cobalt, early thyroidal uptake was depressed and the thyroidal radioactivity accumulated at 16 minutes was discharged by NaSCN. In three of six subjects receiving intravenous cobalt immediately before, and in some cases immediately after, intravenous I^{131}, there was a depression of early thyroidal uptake and partial discharge of accumulated thyroidal I^{131} by NaSCN. These results demonstrate that the action of cobalt is to block organic binding of radioiodide by the thyroid.

Results of distribution and excretion studies of $Co^{60}Cl_2$, with and without carrier, in human subjects suggest that under load conditions only about 10% of the administered dose is absorbed. Variations in absorption and in blood and thyroidal cobalt levels may account for the conflicting reports concerning the effect of therapeutic dosages of cobalt on thyroid function in human subjects.

Results of studies with $Co^{60}Cl_2$ in rats yielded no evidence for concentration of cobalt by the thyroid to an extent significantly greater than could be accounted for by the plasma content of the gland.

Juvenile Hypothyroidism with Precocious Sexual Development.—The combination of juvenile hypothyroidism and certain manifestations of precocious sexual development in a 6 10/12-year-old girl is reported. When first examined, at the age of 7 10/12 years, urinary gonadotropin was elevated to adult levels, and 30% of the cells in the vaginal smear were of the cornified squamous variety. Biopsy of enlarged cystic ovaries disclosed findings similar to those in the ovaries of adults with the Stein-Leventhal syndrome or in response to administration of gonadotropin. The patient became euthyroid during treatment with desiccated thyroid.

Although periodic vaginal bleeding then ceased and the vaginal smear no longer contained cornified squamous cells, the enlarged nipples did not regress and increased excretion of urinary gonadotropin continued.

Journal of Pediatrics, St. Louis
Abstracted by Demetrius G. Traggis, M.D.

53, No. 5 (Nov.) 1958

Serum and Urine Amino Acids in Infantile Toxicosis. C. Choremis and D. Nicolopoulos.—p. 515.
Bronchopulmonary Sequestration in Infancy and Childhood. C. L. Warner, R. L. Britt, and H. D. Riley Jr.—p. 521.
Serum Bilirubin Levels in the Newborn Infant and Their Relation to Clinical Icterus and Liver Function Studies. M. Bogin, S. P. Gottfried, N. V. Levycky, and C. Graf.—p. 529.
Flora of the Umbilical Stump. J. P. Fairchild, C. D. Graber, E. H. Vogel Jr., and R. L. Ingersoll.—p. 538.
Rheumatic Pneumonitis: Part II. Report on the Clinical and Laboratory Findings in Twenty-Three. D. Goldring, M. R. Behrer, G. Brown, and G. Elliott.—p. 547.
Right Heart Catheterization in Infants and Children. B. W. Fink, A. J. Moss, F. H. Adams, and B. J. O'Loughlin.—p. 566.
Acute Upper Respiratory Disease: Clinical and Bacteriological Response to Short-Term Treatment with Penicillin V. J. E. Wheeler, R. F. Plotkin, D. Fromme, and N. Smith.—p. 571.
Studies in Human Reproduction: III. The Frequency of Congenital Malformations in the Offspring of Nondiabetic and Diabetic Individuals. A. Rubin, and D. P. Murphy.—p. 579.
Cerebral Angiomatosis. A. M. Gerhard and H. E. Thelander.—p. 586.
Meconium Peritonitis Caused by a Rupture of a Meckel's Diverticulum in a Newborn Infant. E. F. Gilbert and J. R. Rainey.—p. 597.
* Multiple Hepatic Abscesses Due to Ascaris Lumbricoides. George Thannisch.—p. 602.
Cicatricial Stenosis of the Esophagus Following Ingestion of a Single Urine-Sugar Reagent Tablet. E. J. Tomsovic and H. Javid.—p. 608.
The Children's Medical Center, Boston, Mass.—p. 615.
Medicine at an American Indian Reservation. L. G. Bush.—p. 622.
Adenovirus Pneumonia. R. J. Blattner.—p. 631.

53, No. 6 (Dec.) 1958

* Recognition and Treatment of Adrenal Crises in the Newborn Infant. R. G. Scherz and L. J. Geppert.—p. 645.
The Circulating Eosinophil Level in the Newborn Infant Following Normal and Difficult Labor. M. Khalil.—p. 662.
The Use of Deanol in the Treatment of Disorders of Behavior in Children. L. Oettinger, Jr.—p. 671.
Oleandomycin, a Laboratory and Clinical Evaluation. R. Koch and L. D. Asay.—p. 676.
Glycogen Storage Disease. R. Wagner, N. Meyerriecks and R. Sparaco.—p. 683.
The Role of Candida Albicans in the Common Skin Disorders of Infancy and Early Childhood. A. J. Vignec.—p. 692.
Acute Gastroenteritis. J. G. Armstrong.—p. 704.
Empyema in Children. B. Lionaski, S. W. Gray, and J. E. Skandalakis.—p. 719.
Celiac Disease: Response to a Gluten-Free Diet. S. N. Graven and E. J. Tomsovic.—p. 726.
Cerebral Arteriovenous Fistula Producing Cardiac Failure in the Newborn Infant. A. Q. Pollock and P. A. Laslett.—p. 731.
Methemoglobinema Associated with Intestinal Strangulation Obstruction in the Newborn Infant. W. W. Quillian, J. W. Lancaster, and H. C. Davis.—p. 737.
Coproliths (Calcified Appendiceal Calculi) in Children. F. C. Stiles.—p. 741.
The Children's Medical Center.—p. 744.
Neurologic Complications of Asian Influenza. R. J. Blattner.—p. 751.

Multiple Hepatic Abscesses Due to Ascaris Lumbricoides.—The author reports an unusual complication of Ascaris lumbricoides infection. The patient was a 2½-year-old Negro girl who was admitted with a history of severe abdominal pain, anorexia, lethargy, low-grade fever, and weight loss (10 lb.). She and her siblings were known to have passed long, round worms. Physical examination revealed a temperature of 103 F, the appearance of acute and chronic illness, loss of subcutaneous fat, protuberant abdomen, absent bowel sounds. Laboratory studies revealed Hbg. 10.4 gm.; WBC 23,900, with 33% eosinophils, 32% neutrophils, 30% lymphocytes, 5% monocytes, Ascaris ova and adult worms in stool. X-ray of abdomen did not reveal free air. She was treated with antibiotics and antihelminthics and improved. On the seventh day her temperature was still a little elevated and a mass, thought to be liver was first felt 4 cm. below right costal margin. The mass continued to enlarge and by the 25th hospital day was 8 cm. below costal margin, and a separate nodule was felt in left upper quadrant. Operation was performed, and both lobes of the liver were found to contain multiple, yellowish-gray, indurated areas varying in size from 1 to 3 cm. (13 nodules seen). One nodule was excised. Lymphadenopathy was found about the porta, superior

mesenteric vessels, and left renal vessels. A wound infection developed postoperatively, and the patient slowly recovered. Liver function studies were essentially normal except for a slight elevation of alkaline phosphatase. The pathological specimen showed abscess cavities lined by granulation tissue covered over the inner aspect by necrotic and degenerating polymorphonuclear exudate and debris. Ascaris ova were embedded in the material; the only part of the adult worm left was the cuticle.

The author mentions other reports of the same condition and discusses the pathogenesis, clinical findings and treatment.

Recognition and Treatment of Adrenal Crises in the Newborn Infant.—The authors report four cases of adrenal crisis in newborns due to the adrenogenital syndrome. Three of the four were males. Two males and one female were from the same family, calling attention to the hereditary aspects of the disease. There were two deaths, both were males. The initial symptoms were usually vomiting (often projectible), lethargy, gray, ashen appearance, and collapse. None of the four had symptoms before the seventh day of life. Dehydration, ashen color, collapse, hypotension were the chief findings. The female child showed pseudohermaphroditism. One of the males, by the 12th day, showed an enlarged penis with pigmentation of the scrotum. Another male showed increased pigmentation of the scrotum by the seventh day. The third male (Case 1) showed no abnormalities of the genitalia at 3 months of age but he had been under treatment for 10 weeks (admitted for discontinuation of the fluorodihydrocortisone because of a personal communication from Dr. Lightwood reporting development of hypertension from this drug). The characteristic chemical abnormalities of low serum sodium and chlorides and elevated potassium were present. Main features of treatment in order of importance were (1) salt, (2) DOCA and (3) cortisone. Guides as to the efficiency of treatment were serum electrolytes and urinary 17-ketosteroids and pregnanetriol. When the latter two measurements are normal, the patients were in good control. Because of the need for relatively greater amounts of DOCA for control than adults with Addison's disease need, the authors believe that the disease in infants is actually due to the secretion of a "salt-losing hormone." It was noteworthy that their patients were in very delicate balance, and the discontinuation of salt or DOCA led to an acute crisis. The two deaths occurred when DOCA was discontinued. It was also found that often the necessary dosage of DOCA led to some hypertension which was unavoidable. They also noted that in the beginning it was necessary to use intramuscular cortisone because oral did not control the patients well. Suggested dosages were (1) DOCA 1-4 mg. daily, (2) cortisone 25-50 mg. daily, and (3) salt 3 or 4 gm. a day after the acute crisis is over.

Medical Journal of Australia, Sydney
Abstracted by George H. Lowrey, M.D.

2, No. 12 (Sept. 20) 1958

Extradural Haemorrhage in a Young Child. W. D. Walker.—p. 390.

2, No. 13 (Sept. 27) 1958

The Pyloric Canal Urinary Bladder and Perineum of New-Born Infants. J. B. Cleland.—p. 420.

2, No. 15 (Oct. 11) 1958

* Intravascular Gas in the Radiological Diagnosis of Foetal Death in Utero. Paul Ross.—p. 495.

2, No. 18 (Nov. 1) 1958

The Asthmatic Child. D. G. Hamilton.—p. 589.

A Study of Results Obtained at the Asthma Clinic, School Medical Service, N. S. W. Department of Public Health. Noel Solomons.—p. 592.

* A Social Study of Burns and Scalds in Children. Howard Williams, Nancy Bowman, and Gudrun Malare.—p. 599.

2, No. 20 (Nov. 15) 1958

Pigeon Chest (Protrusion Deformity of the Sternum). Russell Howard.—p. 664.

2, No. 22 (Nov. 29) 1958

Erythroblastosis Foetalis Due to O-A Incompatibility. J. Grantley Shelton.—p. 734.

2, No. 23 (Dec. 6) 1958

The Problem of Apprehension in the Rh-Negative Mother. Vera I. Krieger.—p. 775.

2, No. 24 (Dec. 13) 1958

Further Observations on Infection with Phage Type 80 Staphylococci in Australia. Phyllis M. Rountree and Mary A. Beard.—p. 789.
An Unusual Case of Intussusception. V. H. Hegarty.—p. 801.

Intravascular Gas in the Radiological Diagnosis of Foetal Death in Utero.—The author states that the radiographic signs of gas in the circulatory system of the fetus is absolute indication of death of the fetus in utero. The author states from a review of the literature and his own experience that gas can be visualized in cases of fetal death in utero as frequently as can other signs of maceration. He states that it occurs in about one-half of intrauterine deaths and that the gas usually appears earlier than signs of maceration. The duration of time from death until the appearance of gas is not known certainly; however, it probably takes about three to four days. The origin of the gas is not known. Although this gas has been shown to be present in the vessels of the head and neck, the heart and lungs, the abdomen, and the extremities, and also in the umbilical cord, the most characteristic appearance is in the rounded lobulated shadow found in the heart and in the tree-like shadow of the gas in the vessels of the liver. Several illustrations of radiologic evidence of this gas are shown in the article.

A Social Study of Burns and Scalds in Children.—A one-year study of the cause and types of burns found in children seen in a hospital in Melbourne, Australia, was made. The conclusion reached by the authors were as follows:

1. Accidental burning and scalding of children is a considerable community problem. The Royal Children's Hospital, Melbourne, treats between 500 and 600 children with burns or scalds each year, and over one-third of them require inpatient treatment.

2. Two-thirds of the children are under the age of 4 years. Boys are affected more than girls (ratio 3:2), and scalds are commoner than burns (ratio 7:5).

3. Approximately 90% of the accidents occur in the home, 50% of them in the kitchen. Scalds are most commonly caused by the child reaching and pulling or upsetting a container with hot fluid. Burns are caused by a wider variety of accidents, from touching or falling against an unguarded stove or fire, to burns by chemicals, explosives, or the sun.

4. The majority of these accidents occur in apparently normal family homes in all strata of society. Negligence or carelessness by the mother, and emotional disturbance in the mother or child are responsible for a minority of the accidents.

5. Most of the parents who are involved in these accidents had received no education or information concerning these matters.

6. It was considered that most of these accidents were preventable and that prevention will be achieved principally through better education of the parents.

Monatsschrift für Kinderheilkunde
Abstracted by Hans Hartenstein, M.D.

106, No. 5 (May) 1958

Therapy of Acute Hemorrhage in Childhood. H. Haupt.—p. 245.
° The Quantitative Sensitivity of Antibiotics to Strains of E. Coli Causing Dyspepsia During 1957. L. Tóth and A. Vörös.—p. 251.
Potassium Metabolism of Healthy Infants During the First Three Months of Life. Egon Werner.—p. 254.
First Clinical Results with a New Bilirubin Loading Test. F. M. G. Otto.—p. 257.
BCG Vaccination in Prematures. Friedrich Eckardt.—p. 261.
Prenatal Pediatrics. Gerhard Martius.—p. 263.
Ovarian Hemorrhage, Especially from Corpus Luteum Cysts, as a Cause of Acute Abdomen in Childhood. Waldemar Ch. Hecker.—p. 269.
Pre-Mortem Diagnosis of Generalized Cytomegalic Inclusion Disease. Ulrich Keuth.—p. 272.

106, No. 6 (June) 1958

Latent Hypovitaminosis A in Artificially Fed Infants. W. Kuebler.—p. 282.
° Artificial Infant Feeding and Vitamin A Content. H. Rind.—p. 285.
Poisonings in Childhood: Poison Control Centers. W. T. Bruns.—p. 289.
Relationships Between Maternal and Fetal Endocrine Secretions During Pregnancy. E. Thomas.—p. 291.
Statistical Experiments Regarding Loudness of Cardiac Sounds. Paul Heintzen.—p. 294.
Diagnostic and Prognostic Significance of Repeated Intracutaneous Tuberculin Tests. I. Simkó and K. Lother.—p. 298.
Chyluria. F. Hilgenberg and H. Dransfeld.—p. 300.
Pediatric Surgery. Fritz Rehbein.—p. 306.

The Quantitative Sensitivity of Antibiotics to Strains of E. Coli Causing Dyspepsia During 1957.—At the Children's Clinic of the University of Pécs, Hungary, 157 strains of E. coli causing infantile dyspepsia were tested for antibiotic sensitivity. During an outbreak in 1951 it was found that they were sensitive to Chloromycetin and Terramycin. However, during another epidemic in 1957 they were resistant to Chloromycetin, Aureomycin, Streptomycin and Terramycin. Only Neomycin was found to be effective.

Artificial Infant Feeding and Vitamin A Intake.—In testing various forms of artificial infant feeding preparations used in Germany, it was found that vitamin A content varied markedly among them and did not satisfy requirements for the first year of life.

It was suggested that infants receive supplemental sources of vitamin A during the first year of life, preferably a water-soluble ester.

New England Journal of Medicine, Boston
Abstracted by Demetrius G. Traggis, M.D.

259, No. 15 (Oct. 9) 1958

Patterns of Breast Feeding: I. Factors Affecting the Frequency of Breast Feeding in the Newborn Period. E. J. Salber, P. G. Stitt, and J. G. Babbott.—p. 707.

* Acute Meprobamate Poisoning. L. W. Powell Jr., G. T. Mann, and S. Kaye.—p. 716.

Leukemia in an Infant Born of a Mother with Leukemia. H. C. Cramblett, J. L. Friedman, and S. Najjar.—p. 727.

Septic Thrombophlebitis with Septicemia: Report of Three Cases Due to Staphylococcus Aureus Infection After the Intravenous Use of Polyethylene Catheters for Parenteral Therapy. R. W. Phillips and J. D. Eyre Jr.—p. 729.

Current Concepts in Therapy.—p. 732.

259, No. 21 (Nov. 20) 1958

Demethylchlortetracycline: A New Tetracycline Antibiotic That Yields Greater and More Sustained Antibacterial Activity. C. M. Kunin and M. Finland.—p. 999.

Effectiveness of Influenza Vaccines During an Epidemic of Asian Influenza. B. F. Gundelfinger, W. T. Stille, and J. A. Bell.—p. 1005.

* The Inadequacies of Routine Bleeding and Clotting Times. L. K. Diamond and F. S. Porter.—p. 1025.

259, No. 23 (Dec. 4) 1958

* Primary Hyperoxaluria and Oxalosis: Report of a Case and Review of the Literature. John T. Godwin, Major F. Fowler, Eleanor F. Dempsey, and Philip H. Henneman.—p. 1099.

Boric Acid Poisoning in an Infant. John P. Connelly, John D. Crawford, and Albert H. Soloway.—p. 1123.

Acute Meprobamate Poisoning.—The authors discuss the pharmacology and toxicology of meprobamate and report two fatal cases of ingestion of it as means of suicide. Experimentally the drug has three properties relating to its usefulness: a muscle relaxant action, an anticonvulsant action (protecting mice against toxic doses of pentylenetetrazole), and a taming effect on monkeys. The diaphragm is relatively resistant to the drug. The action is a blocking effect on interneurons (which has been demonstrated in the spinal cord) and a selective action on the thalamus. The LD_{50} for mice is 800 mg/kg. intraperitoneally. Monkeys given up to 600 mg/kg. orally developed a fluid paralysis lasting more than seven hours, but pulse and respiration were normal and recovery was complete.

Two suicides were reported in a 43-year-old and 25-year-old woman. Drug dose was estimated as 240 and 350 mg/kg. Autopsy on one was essentially negative, whereas the other showed pulmonary congestion and cerebral edema. A review of the literature revealed 11 cases of ingestion. Stupor and coma were consistent findings; shock or low blood pressure or pulse was seen in several; areflexia was often seen, and respiratory collapse was occasionally seen. Treatment would appear to be the use of CNS stimulants (caffeine, picrotoxin, pentylenetetrazol), I. V. fluids with vasopressor substances and oxygen. Because of the flaccidity overhydration should be avoided.

The Inadequacies of Routine Bleeding and Clotting Times.—The authors report their experiences with three groups of patients on whom routine bleeding and clotting times had been determined preoperatively in order to screen out those who were "bleeders." Routine tests were those of bleeding time by the Duke or Ivy method, and clotting time by the Lee-White method or capillary tube method. The first group of nine patients were referred to them because other laboratories had reported abnormal studies. Their tests, which included peripheral blood examination, bleeding time by Ivy method, clotting time by Lee-White method,

Quick prothrombin time, prothrombin consumption, thromboplastin-generation test, and direct capillary microscopy, were negative as was the family and past history.

The second group of eight had had normal values but had bled after operation. Their bleeding studies were normal in spite of the bleeding postoperatively. The third group consisted of 19 patients who had had normal bleeding and clotting times even by the authors' tests but when special tests (prothrombin consumption and thromboplastin generation) were done, 12 proved to have classic hemophilia, and 7 Christmas disease. All had positive family and past histories.

The authors point out the inadequacies of the usual bleeding and clotting methods. They are much opposed to the use of the ear lobe in bleeding-time determination, having seen severe bleeding that was uncontrollable by pressure. The authors feel that the routine tests done before surgery to screen "bleeders" are not only useless but misleading, and that a careful history is most important to pick up the mild forms of the various coagulation defects.

Primary Hyperoxaluria and Oxalosis.—The authors report the 27th case of a rare disease termed "oxalosis" to call attention to the possibility of this disease in patients with renal stones.

The patient was a 10-year-old boy when he died. He was well until 5 years of age, when he passed a renal calculus. X-ray revealed bilateral renal calculi. From then until his last admission, he passed many stones and suffered from recurrent infections of the G. U. tract.

There was no history of disease in the parents. An older brother died at age 6½ years from "glomerulonephritis" and anemia, apparently suffering from the age of 6 months with glomerulonephritis and pyuria. One aunt at age 28 years had a stone removed from one kidney.

At age 8 years patient was admitted to the hospital with a weight of 45 lb. and height of 47½ in. P. E. neg. Urine showed spec. gr. 1.010, pH 5.0, + albumin, occasional clumps pus cells, 14-30 RBC/h. p. f., and 10-15 calcium oxalate crystals. PSP 85% in two hours. Chemical analysis of several renal stones gave a + test for uric acid and a 4+ test for calcium oxalate. Six 24-hr. urine specimens contained 130-180 mg. of oxalate/24 hr. (Normal: 18 adults and two 8-year-old children, 15-50 mg.)

X-ray revealed calcifications that outlined contours of renal pelves and calyxes. He was admitted a year later (9 years old) showing progressive renal failure and admitted the last time at 10 years of age, at which time he died in renal failure. The most significant finding at autopsy was in the kidneys, which contained large numbers of calcium oxalate crystals, especially in the cortex. Some crystals were also found in cartilage, pancreatic acini, pulmonary alveoli, myocardium, lymph nodes, adrenal cortex, hepatic arteriole and thyroid gland. A large amount was found in the thymus. The kidney contained 31.0 gm. of calcium oxalate/100 gm. renal tissue.

In their discussion the authors refer to the work of others on oxalosis, bringing out the fact that on the usual diet oxalate ingestion is insufficient to be important in the etiology of renal calculi. Most workers believe that primary hyperoxaluria, as in this case, has a hereditary background and is an inborn error of metabolism.

Pediatriya, Moscow

Abstracted by Moses Grossman, M.D.

36, No. 8 (Aug.) 1958

Current Problems of Tuberculosis of Early Childhood. I. V. Tsimbler.—p. 3.
Toxicoinfection Sensitization Problems in Children. Otakar Teishl.—p. 8.
* Alteration of Total Spinal Fluid Protein and Protein Fractions in Tuberculous Meningitis. I. V. Mchedlishvili.—p. 18.
Acid Base Balance in Older Children with Chronic Pneumonia. A. A. Ananenko.—p. 52.

36, No. 9 (Sept.) 1958

Changes in Skin Temperature and Sweat Secretion in Acute Pneumonia in Infants. N. N. Rubina.—p. 18.
Neurological Changes in Children with Rheumatic Fever. N. Ilyash.—p. 36
The Clinical Picture of Arthritis Deformans Endemica (Kashin-Beck) Syndrome. E. N. Kalinovskaya.—p. 42.
Sedimentation Rates in Normal Children of Various Ages. I. A. Ionova.—p. 62.

36, No. 10 (Oct.) 1958

The Pathogenesis of Rickets. K. A. Svyatkina.—p. 9.
Hygienic Assessment of Collection and Quality of Breast Milk in a Breast Milk Bank. E. E. Kachanova, M. A. Gorbacheva, N. A. Petrachenko, and A. N. Kholodok.—p. 14.
Blood Vitamin A and Carotene Levels in Normal Infants in the First Year of Life. F. A. Zverkova.—p. 20.

Serum Protein and A/G Ratio in Tuberculosis in Children. V. A. Sheshina.—p. 26.
Significance of Extoxin and Allergen of the Hemolytic Streptococcus in the Pathogenesis of Scarlet Fever. T. M. Yakimenko.—p. 32.
A New Method of Managing the Umbilical Cord. N. M. Dorofeef.—p. 52.
Congenital Agammaglobunemia: Case Report. I. I. Balashova.—p. 67.

36a, No. 11 (Oct.) 1958

* Use of Na Salicylate in the Treatment of Eczema. G. N. Guzhienko and M. M. Chekodanova.—p. 7.
Kaposi's Varicelliform Eruption—Report of Eleven Cases. E. L. Kifer.—p. 13.
Diagnosis and Treatment of Hemangioma in Children. N. I. Kondrashin.—p. 23.
Ovarian Tumor in Children. V. D. Kurov.—p. 27.
Studies of Thyroid Function in Children with the Use of Radioactive Iodine. L. F. Berezhkov.—p. 32.
Treatment of Acute Dysentery in Children with Combined Chemo and Immunotherapy. R. A. Tyurkyau.—p. 41.
Ketosteroid Secretion in Children with Rheumatic Fever. T. P. Borisova and E. G. Larsky.—p. 46.

36, No. 12 (Dec.) 1958

* Clinical Manifestations of Present-Day Rheumatic Fever in Children. Z. I. Edelman.—p. 7.
Phonocardiography in Children. K. P. Sarylova.—p. 13.
Diagnostic Significance of the Opening Snap in Mitral Stenosis. M. K. Oskolkova.—p. 17.
Radiological Data on the Development of Mitral Valve Disease in Children. M. M. Deeva.—p. 22.
* Clinical Features of Influenza A_2 in Infants. S. A. Bayandina.—p. 38.
Viral Influenza in Children. V. M. Afanasieva.—p. 49.
Phagocytic Activity of Leukocytes in Some Infectious Diseases. E. V. Sergueva.—p. 59.
Health Protection of Women and Children in the White Russian SSR. M. M. Tur.—p. 75.

Alteration of Total Spinal Fluid Protein and Protein Fractions in Tuberculous Meningitis.—Fifty-one children with tuberculous meningitis had serial studies of spinal fluid protein, including A/G ratio of the protein. Characteristically, the spinal fluid protein was elevated, the main rise being in the globulin fraction.

The A/G ratio is more important prognostically than the total protein content. A very low A/G ratio is a bad prognostic sign, and generally correlates with low spinal fluid sugar levels. Change in the A/G ratio of spinal fluid protein might also be the first sign of an impending relapse.

Use of Na Salicylate in the Treatment of Eczema.—The authors followed Dr. Woringer's suggestion for using Na salicylate for the treatment of infantile atopic eczema. Fifty children were studied. Of the 50 patients 28 were under 1 year of age. Most of the cases were very severe, many complicated by superinfection. The usual dietary regime was used, local skin care included various accepted ointments, including antihistamine and hydrocortisone ointment. Antibiotics were used as needed. The dose of Na salicylate supplied was 0.1 gm. per kilogram body weight in divided doses. The first affect was decrease in itching followed by improvement of skin condition. The authors were impressed that Na salicylate provided a useful adjunct to treatment of eczema.

Comment: The authors missed an opportunity to run a control series of patients. The variety of dietary and environmental regimen used is such that it would be impossible to evaluate Na salicylate objectively from this report.

Clinical Manifestations of Present-Day Rheumatic Fever in Children.—A review is presented of 1,711 children with rheumatic fever seen over the last eight years, and the results are compared with series in former years. Of these children 63.6% were admitted with their first attack of the disease; 38% of the total group were under 8 years; 10% were between 2 and 5 years. There has been a recent increase in incidence of rheumatic fever in the younger age group. The number of children showing cardiac involvement has increased to 60.7%; the incidence of joint involvement has fallen from 75% to 28.8%. The incidence of nodules has dropped from 14.5% to 5.2%; erythema annulare is now found in 4.3% of cases. The severity of the disease as a whole, and of cardiac involvement in particular, has decreased in recent years—dropping the mortality from 8.9% to 1.6%. In the last three years, mortality during the first attack has been only 0.43%. The factors at play in these changes in the natural history of the disease are discussed.

Clinical Features of Influenza A_2 in Infants.—Between October and November, 1957, 26 infants were situated on the infant wards of First Moscow Institute. Of these 22 developed Influenza Type A_2. All four of the infants who did not develop the disease had had it immediately prior to admission, which was necessitated by complicating pneumonia. The outbreak was caused by admission of seven acute cases of influenza. The ward was then

placed in quarantine. Of the 22 cases 18 were confirmed by virological, serological studies; 10 of the infants had primarily respiratory symptoms, many with interstitial pneumonia. In the other 12 infants, the first symptoms were respiratory ones, but they were followed by gastrointestinal tract disturbances which dominated the picture. Many infants had a second febrile episode after one to two days of subnormal temperature. Many children had abnormal urinary findings.

All infants excreted virus from the nasopharynx for 10-15 days. Antibody rises as determined by hemagglutination and complement-fixation were of low titer compared with adults.

These infants were treated with influenza A_2 anteserum administered intranasally. This therapy was augmented by administration of γ-globulin, maternal blood, parenteral fluids, and antibiotics for complications. There was one death in a 5-month-old premature infant, who also had rickets and severe pneumonia.

Abstracts from the Soviet Literature

A selection of abstracts drawn from the current issue of Abstracts of Soviet Medicine, *a quarterly journal published by the Excerpta Medica Foundation (New York Academy of Medicine Building, 2 E. 103d St., New York 29), with the aid of a grant from the U. S. Public Health Service.*

Gastrointestinal System

Congenital stenosis of the oesophagus in children (O vrozhdennykh stenozakh pishchevoda u detei). Bairov, G. A. and Trofimova, Z. A. Pediatric Institute, Leningrad *Vopr. Okhr. Mater. i Dets.* 1958, 1 (7-10).

Six cases of congenital stenosis of the oesophagus in children and corresponding literature data are analysed. The most frequently encountered form of congenital stenosis in children is annular stenosis. The membranous form is rare. Radiological examination establishes the diagnosis in annular stenosis. Oesophagoscopy is essential for the diagnosis of the other forms of stenosis. Roentgenological features characteristic of congenital stenosis are narrowed lumen of the oesophagus with even contours, normal relief of the mucosa and absence of spasm in the narrowed part of the oesophagus. Bouginage is recommended as treatment.

Respiratory System

The state of the cardiovascular system in chronic pneumonia in children (Sostoyanie serdechno-sosudistoi sistemy pri khronicheskoi pnevmonii u detei). Tserkovnaya, L. N. Sechenov First Medical Institute, Moscow *Pediatriya* 1958, 1 (55-60).

Fifty children suffering from chronic pneumonia were under observation. Studies of the cardiovascular system revealed that it was affected in all forms of chronic pneumonia in children. The main manifestations of disturbances of the cardiovascular system were: pallor; cyanosis; instability of pulse; change in size of heart, either diminution or enlargement; apical systolic murmur; accentuation of the second sound over the pulmonary artery; disturbances of arterial and venous blood pressure and changes in a number of functional tests revealing the reserve capacity of the cardiovascular system; changes in the ECG and in capillary circulation. These abnormalities are most marked in bronchiectasis. Cardiovascular changes usually increase with every exacerbation of the illness and are absent on clinical recovery.

Sudden death in early childhood (O skoropostizhnoi smerti v rannem detskom vozraste). Avakyan, N. M. *Sborn. Trud. Byuro Glavn. Sudmed. Ekspert. i Kaf. Sud. Med. Yerevan. Med. Inst.* 1956, 1 (83-91).

According to the data of forensic expertise in Erevan, sudden death in childhood forms 33-35% of all sudden death cases in the population. The author investigated the autopsy material of 57 such cases in children aged from 10 days to 3 years; in this series the prime cause of death was pneumonia (65-70%). Bacteriologic examinations of the autopsy material demonstrated most frequently pneumococci, then streptococci and staphylococci.

Sudden death in early childhood from interstitial pneumonia (Skoropostizhnaya smert v rannem detskom vozraste ot interstitsialnoi pnevmonii). Avakyan, N. M. and Beglaryan, A. G. *Sborn. Trud. Byuro Glavn. Sudmed. Ekspert. i Kaf. Sud. Med. Yerevan. Med. Inst.* 1956, 1 (114-123).

The respiratory organs of 75 children, victims of sudden death, were examined. It was found that interstitial pneumonia is not a rare condition in small children in cases of sudden death

(15 of the 75 cases). Interstitial lesions were found together with catarrhal, desquamative tracheo-bronchitis and bronchiolitis. The pulmonary alveoli were found contracted. The inflammatory process spreads readily in the interstitial spaces, followed by severe haemodynamic and infiltrative-exudative changes, leading to impairment of gaseous exchange and asphyxia.

Acute Infectious Diseases

The importance of streptococcal allergy in scarlet fever (Znachenie streptokokkovoi allergii pri skarlatine). GALPERIN, E. A. Clinic of Infectious Diseases, Central Postgraduate Institute, Moscow *Pediatriya* 1957, 8 (19-24) Tables 2.

Sensitization to streptococci detected by tests with allergens develops in patients with scarlet fever during their hospitalization. This allergic condition runs a subclinical course. Scarlet fever is a monocyclic infection which can be complicated by exogenous infections; complications depend on the conditions of placement of the patients (private or general wards). Administration of penicillin as a rule clears these secondary infections. Suitable precautions are indispensable during the treatment of scarlet fever not only for the prevention of infectious complications but also in order to increase the non-specific resistance of the constitution.

Clinical picture of diphtherial paralysis (K klinike difteriinykh paralichei). BELAYA, N. K. *Pediatriya* 1957, 1 (41-44).

Ninety children with toxic diphtheria of the throat, who developed paralysis, were under observation. Mortality was 10%. Diphtherial paralysis was more frequent in children between 2 and 5 years (24.3%); the author explains this as due to more frequent toxic forms of diphtheria at that age. In the subtoxic form of diphtheria paralysis was present in 5.6% of cases. In the toxic form grade I they were twice as frequent, in the toxic form grade II almost six times as frequent, and in the toxic form grade III eight times as frequent. The frequency of paralytic complications of diphtheria was in direct relation to the severity of the disease. Paralysis of soft palate was most frequent, then paresis of lower limbs and paresis of abducent nerve. In the majority of cases paralysis developed in the 2nd to 3rd week (54.6%), rarely during the first week (1.8%); late paralysis (during the 4th to 6th week) occurred in 32.7%. Causation of secondary waves of paralysis remains obscure. There was no obvious influence of intercurrent infections on the course of paralysis.

Chronic Infectious Diseases

Some data on the relation between the forms of infection and clinical incidence of tuberculosis in young children (Nekotorye dannye o sootnoshenii form infitsirovannosti i porazhennosti tuberkulezom detei rannego vozrasta). RACHINSKII, S. V. Pediatric Institute, USSR Academy of Medical Sciences, Moscow *Pediatriya* 1958, 1 (7-14) Ref. 22.

In most cases a positive Pirquet reaction with a papule measuring 5 mm. and over in infants indicated the presence of tb infection and was not a manifestation of post-vaccination allergy. In the case of children with papules measuring less than 5 mm. in diameter half their number go on to being tuberculin-positive. Severe forms of tb (haematogenic-disseminated, miliary and meningeal) comprise only 6% of the total number of cases, whereas 33.4% are made up of forms without marked localization (early tuberculous toxaemia). Mortality among children in 1955-1956 was 0.47%.

Conditioned and unconditioned vascular reflexes in children with tuberculous meningitis (Uslovnye i bezuslovnye sosudistye refleksy u detei pri tuberkuleznom meningite). MOSHCHITS, P. S. Department of Pediatrics, Medical Institute, Kiev *Pediat. Akush. i Ginek.* 1957, 2 (20-25) Illus. 4.

An investigation of conditioned and unconditioned vascular reflexes was conducted on 40 patients with tuberculous meningitis. In the acute stage of the disease vascular reflexes were depressed or absent (the plethysmogram approached a straight line). This may be associated with a diffuse inhibition spreading from the cerebral cortex to the lower vasomotor centres. With improvement in general condition there is a gradual de-inhibition of the subcortical centres and the primitive unconditioned reflexes reappear, characterized by little depth and 'inertia' of development. After disappearance of the meningeal syndrome the unconditioned reflexes become more efficient and the formation of conditioned vascular reflexes becomes possible. A delay in the return of vascular reactions to normal is prognostically unfavourable. A complete return of vascular reactions to normal was not, however, observed at the time of

recovery. Plethysmograms taken in the stage of complete recovery still lack stability and constancy.

Protein and protein fractions content during the active phase of the cardiac form of rheumatic disease in children (Dinamika belka i belkovykh fraktsii v aktivnoi faze pri serdechnoi forme razvitiya revmatizma u detei). KLAISHEVICH, G. I. Central Postgraduate Medical Institute, Moscow *Pediatriya* 1958, 1 (68-74) Ref. 20.

The results are reported of the investigation of total protein and protein fractions content of serum in 44 children aged from 5 to 14 years. The determinations were carried out by means of paper electrophoresis. It was found that, regardless of the amount of total protein during the initial acute period of the rheumatic process, its content increased during the attack in most cases, a.o. by virtue of increased gamma-globulins. Impairment of circulation with the presence of oedema is accompanied, as a rule, by reduction of total protein. The concentration of albumin is lowered in children in the active phase of rheumatic disease and depends on the activity of the process and severity of illness. The amount of albumin rises as the rheumatic process becomes less active. Increased concentration of gamma-globulin serves as an index of the activity and severity of the rheumatic process. Persistent and marked increase in gamma-globulin content is observed with impaired circulation and admixture of a septic component. It is shown that the disturbances of total protein and protein fractions content are determined not only by the condition of the blood vessel walls but depend also on disturbance of processes of synthesis and breakdown of protein in the interstitial substance of connective tissue and on immunological processes which arise in the child's organism.

Materials on the clinical-immunological characteristics of rheumatism in children (Materialy po kliniko-immunologicheskoi kharakteristike revmatizma u detei). SMIRNOVA, A. M. and ELPERIN, E. Z. *Vopr. Okhr. Mater. i Dets.* 1956, 1/5 (34-39).

The authors determined the concentration of streptococcal antibodies in the blood by the complement-fixation reaction with polysaccharide of streptococcal antigen of haemolytic streptococci of the A-group as well as the concentration of streptococcal antigen in 114 children suffering from rheumatism. Serologic investigations were carried out repeatedly at different phases of the disease. A high content of streptococcal antibodies in the blood of the patients was established at the first attack of rheumatism. The content of streptococcal antibodies was higher in cases of relapses of rheumatism. The production of antibodies was slowed in cases of severe relapse of rheumatism. The investigation of streptococcal antigen in the blood was carried out by the use of the complement-fixation reaction with streptococcal immune serum. The results were positive in 15% of the patients. The results were frequently positive in cases of first attack and of relapses of rheumatism, but more often in cases of severe cases of rheumatism. In some cases a correlation could be established between the changes of the curve of the antigen and of the clinical course of the disease.

An experiment in the study of cortical neurodynamics in children suffering from rheumatism (Opyt izucheniya korkovoi neirodinamiki u detei, bolnykh revmatizmom). TRYNKIN, A. L. and OLKHOVSKAYA, G. S. Clinic of Children's Diseases, Medical Institute, Saratov *Pediatriya* 1957, 2 (18-22) Tables 3.

A study of cortical neurodynamics in children suffering from rheumatism was conducted by means of 'verbal influence'—determination of changes in the electrical sensitivity of the eye under the influence of verbal stimuli, and investigations of changes in the electro-conductivity of the skin under the influence of the same agents. The cases under observation were 30 healthy children, 30 patients in the acute phase of rheumatism, and 20 children in remission. Ages ranged from 8 to 15 years. From the observations it was established that one of the peculiarities of cortical neurodynamics in children suffering from rheumatism is a tendency towards reactions of inhibitory character in response to various stimuli. The 'verbal experiment' revealed, in the acute phase of rheumatism, a considerable weakening of ability to form rapid associations, which persisted during remission in some of the children. Stimulation of the auditory and olfactory receptors in children suffering from rheumatism also indicated an accentuation of inhibitory processes especially during the acute phase of rheumatism. Careful attention to health and its protection in every possible way, during the acute phase of rheumatism, and a gradual transition to normal conditions of life via the sanatorium and special open-air schools are necessary for restoration of function of the higher parts of the central nervous system in children.

Diagnosis of internal leishmaniasis (K diagnostike vnutrennogo leishmanioza). LEBEDEVA, V. A. *Zdravookhr. Kaz.* 1956, 12 (9-13).

A series of observations over a 9-year period in the children's department of Kzyl-Ordy hospital showed that in only 22% of cases of internal leishmaniasis the diagnosis was made in the first month of the illness and that there were a high number of diagnostic mistakes. The early symptoms were a worsening of the general state of the child, blood changes and a mild hepato-splenomegaly which was often not noted until fever had developed. The initial period of fever was taken to be due to the onset of typhoid fever, septicaemia or a septic form of brucellosis. In the chronic phase of the disease disturbance of erythro- and leucopoiesis occurred together with hyperplasia of lymph nodes, liver and spleen and as a consequence of this it was necessary to differentiate internal leishmaniasis from aplastic anaemia, agranulocytosis, leukaemias, reticuloses, etc. Eleven out of 93 cases of internal leishmaniasis were mis-diagnosed as tuberculous processes. With onset of the early non-specific symptoms children were routinely observed in localities where internal leishmaniasis was more or less epidemic and this helped to diagnose the initial form of the illness and to separate actual cases which were in an apyretic phase of the disease.

Surgery, Roentgenology

Cholecystography in children (Kholetsistografiya u detei). MIRZAEV, T. M. *Med. Zh. Uz.* 1957, 3 (40-47).

One hundred ninety children of both sexes were investigated. Cholecystography was carried out in 110 adults as control. The excretion of bile containing iodine takes place with sufficient intensity in cases of relatively minor affections of the liver. The use of bilitrast for cholecystography has proved a valuable and harmless method of supplementing the investigation of children with gastro-intestinal diseases.

Social Medicine, Prevention, Organization

Anti-cross-infection measures in children's wards during the 40 years of Soviet power (Borba s vnutribolnichnymi detskimi zabolevaniyami za 40 let sovetskoi vlasti). ROZANOV, S. N. First Children's Hospital, Moscow *Pediatriya* 1958, 1 (49-54).

In Tsarist Russia cross-infections in children's hospitals were common and reached 12%. Conditions favouring the appearance of hospital cross-infections include: careless history taking, incorrect placing of patients, faulty use of space, faulty use of personnel, incorrect management of children's wards, lack of sufficient attention to some hospital cross-infections and inadequate discipline among the personnel. A sharp drop in hospital cross-infections (down to 0.5%) observed in recent years reflects the advance of Soviet health services. Measures designed to combat hospital cross-infections include: strict recording and notification of diseases, serum prophylaxis, epidemiologic records, constant improvement in qualifications of personnel, strict working discipline of the personnel, efficient utilization of personnel, reconstruction of old buildings and construction of new buildings along the lines of individual isolation.

News and Comment

ANNOUNCEMENTS

Research Support for Problems in Neurophysiology.—Funds are now available for basic or clinical research in neurophysiology, the Dysautonomia Association announced today.

The Association will support research related to the clinical entity known as familial dysautonomia, a disease caused by dysfunction of the autonomic nervous system. It will also support any type of study that might lead to a better understanding of nervous system functions at a basic level as a stepping stone to the understanding of a disease process.

The Association will submit all requests for grants to its medical advisory board for evaluation. Requests should be addressed to Harold M. Newman, President, Dysautonomia Association, 2 W. 46th St., New York 19.

Familial dysautonomia was first described as a clinical entity in 1949 by Riley, Day, Greeley, and Langford, and has acquired the eponym "Riley-Day" syndrome. It is thought to be a congenitally acquired state of genetic origin. It involves the entire nervous system, though the autonomic dysfunction is the most devastating aspect of the disorder.

The Association, which has been supporting Dr. Riley's clinical studies at Babies Hospital, also made its first grants for medical research in 1958.

Robert Fishman, M. D., is investigating the metabolism of the fluids surrounding the brain at the Neurological Institute, Columbia-Presbyterian Medical Center. Basic etiologic studies are being carried out in an interdepartmental project at the University of California School of Medicine, Los Angeles, under the leadership of Leonard M. Linde, M. D. A third study has been undertaken by Alfred M. Freedman, M.D., of the State University of New York College of Medicine, who is working with premature babies on the early development of the autonomic nervous system.

The Association's medical advisory board includes Conrad M. Riley, M.D., Associate Professor of Pediatrics, Columbia University College of Physicians and Surgeons, and Associate Attending Pediatrician, Babies Hospital, Columbia-Presbyterian Medical Center; Sidney Carter, M.D., Associate Professor of Clinical Neurology, Columbia University College of Physicians and Surgeons, and Attending Neurologist, Neurological Institute, Columbia-Presbyterian Medical Center; Alfred M. Freedman, M.D., Professor of Psychiatry, State University of New York College of Medicine, and Associate Visiting Pediatrician, Kings County Hospital; William S. Langford, M.D., Professor of Psychiatry, Columbia University College of Physicians and Surgeons, and Attending Pediatrician, Babies Hospital, Columbia-Presbyterian Medical Center, and Ralph E. Moloshok, M.D., Assistant Clinical Professor of Pediatrics, Columbia University College of Physicians and Surgeons and Assistant Attending Pediatrician, Babies Hospital, Columbia-Presbyterian Medical Center, and Mount Sinai Hospital.

Catalogue of Selected Films on Pediatrics and Child Health.—A new catalogue of films on Pediatrics and Child Health is now available from the A. M. A. Department of Medical Motion Pictures and Television. This catalogue is the result of a long-term reviewing project of the Committee on Medical Education of the American Academy of Pediatrics and the Department of Medical Motion Pictures American Medical Association. Each film title is accompanied by a short description and information necessary to determine its suitability for showings along with its source.

Research Opportunity.—The Johns Hopkins University has a position open in a research laboratory concerned with the pathology of pregnancy and newborn infants. This would be suitable for a pediatrician, an obstetrician, or a pathologist. There will be an opportunity for doing research independently or in collaboration with a senior staff member. The person should also serve as liaison between research in the laboratory and in the clinical service. Those interested should write to Dr. Peter Gruenwald, Department of Obstetrics, The Johns Hopkins Hospital, Baltimore 5.

GENERAL NEWS

Heart Association to Spend $3,300,000 for National Research Support.—The American Heart Association has announced that it will spend a total of approximately $3,300,000 for scientific studies in the field of heart and blood vessel diseases during the 12 months beginning July 1.

According to Dr. Francis L. Chamberlain, President, this is the largest sum ever appropriated by the Association's National Office to support research in a single fiscal year, and represents a commitment of approximately 57% of the income received by the National Office from public contributions to last year's Heart Fund appeal. With the 1959-1960 awards, Dr. Chamberlain pointed out, the total channeled into a scientific research by the American Heart Association and its affiliates since reorganization as a voluntary health agency in 1948 now stands at more than $44,000,000.

Named today were recipients of 244 grants-in-aid, representing the award of $1,765,233. Previously announced was the award of approximately $1,600,000 in fellowships and investigatorships to 180 scientists, including seven career investigators the Association supports on a lifetime basis.

Dr. Chamberlain emphasized that affiliated state and local Heart Associations will make additional research awards for 1959-1960 to scientists not only in their own areas but also throughout the country. In 1958-1959 these totaled approximately $5,500,000, with an increase expected in the forthcoming fiscal year. The Heart Fund has thus become, said Dr. Chamberlain, the largest single private or nongovernmental source of support for scientists seeking answers to the many still-unsolved problems posed by the heart and blood vessel diseases.

Books

BOOK REVIEWS

Pharmacologic Principles of Medical Practice. Fourth Edition. By J. C. Kantz Jr. and C. J. Carr. Price, $14. Pp. 1313, with 89 figures. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Like its predecessors, this book is a concise volume covering adequately the basic aspects of pharmacology. It is well organized, and except for some minor affectations (such as using plasmatic membrane for plasma membrane, nonsensitive for insensitive and numerous didactic definitions), it is also well written. The unique quality of this book is retained, giving a wealth of historical background on the different branches of pharmacology and many portraits of great men in pharmacology and their important contributions. In the organization of the book, a harmonious compromise seems to have been achieved whereby the importance of pharmacodynamic aspects of drug action has not overshadowed the more frequently used drugs in practice whose mechanisms of actions may not be too well elucidated. Thus the antibiotics are accorded a justifiable priority in the early part of the book. Moreover, drugs acting on the skin, those used on the ears, nose and throat, and some drugs acting on the gastrointestinal tract are all discussed in some detail because of their usefulness. The autonomic drugs which form the cornerstone of modern pharmacology are discussed eloquently and in sufficient detail to enable the beginning student to understand them without difficulty. Lastly, the need for this new edition is well satisfied by the inclusion of many new drugs worthy of consideration. There are many examples in the antibiotics, drugs used for treatment of hyperkinetic states, anesthetics, analgesics, etc. The psychotomimetic drugs which are still in a fluid status are impartially and critically summarized in a separate chapter. One annoying defect of the whole book is the inadequate references listed at the end of each chapter. The reader's curiosity is often aroused by a source quotation in the text only to find that it is not listed in the reference.

C. Y. Kao

Chronik der Kinderheilkunde. By Prof. Dr. med. Albrecht Peiper. Price, DM 51.20. Pp. 527, with 97 illustrations. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig C1, 1958.

The latest edition of Peiper's historical review of pediatrics presents an amazing wealth of material. Fortunately it is not restricted to the diseases of children but contains many facts about the life of children throughout recorded history.

History proves again to be a yardstick of progress. The reader of this book—he has to be able to read German—will see the various reasons why our children live today a much better and healthier life than yesterday. It is pointed out how well the parents, the physician, and, not least, the law have learned to protect a child. Ignorance, superstition, and lack of good will were responsible for a very high childhood mortality, which began to decline just in the past 100 years.

On the other hand, the author has demonstrated that loving parents as long ago as 4,000 years B. C. were concerned with the general welfare of their children as much as we are concerned with that of our children today. It was of great interest to this reviewer to read about the various methods of infant nutrition, the ways infants and children were dressed, and the various methods of schooling. Repetitive cycles similar to Spengler's great cycles in history became apparent. The excellent pictorial material illustrates this vividly.

The author has also collected all information regarding early descriptions of the commoner diseases of children. This may be helpful for the authors of nosological papers. A reference to this book may often eliminate lengthy historical reviews, and young pediatricians preparing a case for a clinical conference can easily scintillate with historical knowledge after a quick look into this book.

This reviewer was somewhat disturbed by the occational lack of organization and at times could not avoid the impression that a card index was copied. A bad taste remained after finding a political tincture in some parts of this historical discussion. The author's residence

in East Germany may explain the very lengthy and rather gloomy discussion of child labor in Western societies.

GUNNAR B. STICKLER, M.D.

Uber die Erblichkeit des normalen Elektroencephalogramms. By Dr. F. Vogel. Price, DM 9.60. Pp. 92, with 25 illustrations. Georg Thieme Verlag, Herdweg 63 (14a), Stuttgart N., (American agent—Grune & Stratton, Inc., 381 4th Ave., New York 16), 1958.

In an excellent monograph the author presents a study of the influence of heredity within normal patterns of the electroencephalogram. His series included 208 pairs of normal twins, of whom 110 were monozygotic and 98 dizygotic. Their ages ranged from 6 to 30 years. The electroencephalograms were made on a 16-channel machine permitting the simultaneous recordings from the twin pair with eight leads for each individual. The EEG's were recorded during rest, hyperventilation, oxygen deprivation, and natural sleep.

The parameters measured were the basic rhythm, the alpha index, the subalpha percentage (introduced by the author), the average wave amplitude, the wave continuity, and the phase coordination. An identification test after Travis and Gottlober was performed.

The results indicate that in the resting EEG as well as those taken during hyperventilation and oxygen deprivation there is, with rare exceptions, no constant difference of the cerebral electrical activity in monozygotic twins, whereas such difference is obvious in dizygotics. Also the sleep EEG shows an almost absolute concordance in monozygots. Reexamination of 15 pairs of monozygotic twins carried out one year later likewise revealed no difference of the paired electroencephalograms.

The author concludes that the character of the EEG is determined entirely by genetic factors and that the maturation of those brain functions which are represented in the EEG takes place on a hereditary basis also. Records of monozygotic twins resemble each other as those of the same person. No relationship to handedness was found in this series, and no increased occurrence of homology of the two hemispheres of the brain could be demonstrated.

Dr. Vogel is Dozent at the Max Planck Institute for Comparative Genetics in Berlin, Germany.

JUERGEN E. THOMAS, M.D.

Krankheiten der Neugeborenen. By Prof. Dr. med. Albrecht Peiper. Price, DM 19.40. Pp. 131, with 54 illustrations. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig C1, 1958.

This book, edited by Peiper, contains 13 rather sketchy review articles regarding the newborn period. The papers were written by various authors. Each contribution is followed by a very brief bibliography, which often does not include references to key articles. This reviewer believes the book may be of only local importance. American pediatricians would be bothered by dogmatic statements regarding the necessity of a fixed feeding schedule or a sentence like the following: "The administration of artificial formulas is, in our opinion, for the newborn just as great a stress as a surgical operation." Very informative, however, is one chapter by Strüve on listeriosis of the newborn, which apparently is observed frequently in Leipzig and Halle.

GUNNAR B. STICKLER, M.D.

Recent Advances in Paediatrics. By Douglas Gairdner, M.A. (Cantab.), D.M. (Oxon), F.R.C.P. Price, $9.50. Pp. 378, with 82 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

The authors who contribute to this book are distinguished scientists from America and Great Britain who propose to review the advances and lack of advances in certain fields essential to the further development of pediatrics.

In order to cover subjects in greater detail than was present in the first edition of this volume in 1945, the chapters are reduced to thirteen, covering circulatory changes at birth, hematology of infants, jaundice in the newborn, physical growth, hypothyroidism, spina bifida cystica, hydrocephalus of infancy, the nephrotic syndrome, tuberculosis, rheumatic fever, the deaf child, and pyogenic osteitis.

Each chapter reviews the recent advance of authors throughout the world with excellent references available in each field. The authors attempt to correlate the diversified findings and assemble them in a manner which clearly differentiates established facts from proposed hypothesis.

One who has not been able to keep abreast of current developments in the above-mentioned fields will find an opportunity to read succinct, excellently written comments and thoughts by the authors with enough details to make the reviews worth while and without so much detail as to make the chapters unreadable.

Certainly the first four chapters must be especially cited as being very stimulating to the younger colleagues, yet with enough factual material to satisfy those with more advanced knowledge. The chapter on circulation, written by Geoffrey Dawes, an animal physiologist, again emphasizes the importance of contributions of all the allied sciences in the further development of pediatrics.

The typography and illustrations are adequate and the volume edited by Dr. Gairdner is free of any notable technical errors.

Certainly, those interested in the recent advances in pediatrics will find this book most stimulating and valuable.

SAMUEL T. GIAMMONA

Clinical Epidemiology. By John R. Paul, M.D., Sc.D., Professor of Preventive Medicine, Yale University School of Medicine. Price, $5. Pp. 290, with 37 illustrations. The University of Chicago Press, 58th St. and Ellis Ave., Chicago 30, 1958.

Dr. Paul quickly brushes aside the false notion that epidemiology is a statistical scoreboard of epidemics, their origin and control. He discusses epidemiology as being concerned with "the circumstances under which disease occurs, where diseases tend to flourish and where they do not." His concept of etiology of diseases is discussed in a very interesting way by utilizing agricultural similes of "seed," "soil," and "climate." The "seed" applies to the causes of the disease, whether it be a singular agent or comprised of multiple factors. The "soil" refers to the host and its condition when the seed is sown. The "climate" represents environmental factors which affect the seed and soil interaction.

Separate chapters deal with the history of epidemiology, experimental epidemiology, the statistical methods and measurements commonly used, factors in host susceptibility, geographic epidemiology, vectors, and the socioeconomic factors in disease.

The methods of study are then applied to diseases of rheumatic fever, coronary occlusion, poliomyelitis, infectious hepatitis, and the arthropod-borne viral encephalitides.

"Clinical Epidemiology" is an interesting and readable treatment of an important subject and is recommended reading for all students of medicine.

WILLIAM J. A. DEMARIA

Directory of Pediatric Societies *

INTERNATIONAL

Ninth International Congress of Pediatrics

President: Dr. Allan Ross, P. O. Box 215, Westmount, Montreal 6.
Vice-President: Dr. Albert Guilbeault, P. O. Box 215, Westmount, Montreal 6.
Secretary-General: Dr. R. L. Denton, P. O. Box 215, Westmount, Montreal 6.
Place: Queen Elizabeth Hotel, Montreal. Time: July 19-25, 1959.

International Union for Child Welfare

President: Mr. Leonard W. Mayo, 1, rue de Varembé, Geneva, Switzerland.
Vice-President: Judge M. C. de Jong, 1, rue de Varembé, Geneva, Switzerland.
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FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

President: Dr. J. B. J. McKendry.
Secretary: Dr. J. A. McKee, 2120½ Queen St. E.
Place: Hospital for Sick Children. Meetings: Once a month.

Asociacion de Pediatrías Españoles

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Time: Second and fourth Thursday of each month.

Australian Paediatric Association

President: Sir K. B. Fraser, Ballow Chambers, Wickham Terrace, Brisbane.
President-Elect: Dr. H. McLorinan, Fairfield Hospital, Melbourne.
Secretary: Dr. T. R. Biggs, 33 Wickham, Brisbane.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Dr. J. Forest Smith, 149 Harley St., London, W. 1.
Secretary: Dr. P. R. Evans, Institute of Child Health, Great Ormond St., London, W. C. 1.

Canadian Paediatric Society

President: Dr. Henri Charbonneau, 3095 Sherbrooke St. E., Montreal.
Secretary: Dr. J. A. P. Turner, 305 Bessborough Dr., Toronto 17.

Clinical Pediatric Society of Israel

Chairman: Dr. S. T. Winter, Rothschild Hospital, Haifa.
Secretary: Dr. E. Freundlich, Rambam Hospital, Haifa.
Place: Inter-Hospital. Time: Bimonthly.

Danish Pediatric Society

President: Dr. P. W. Braestrup, Amtssygehuset, Hellerup.
Vice-President: Dr. J. Vesterdal, Bülowsvej 18B, Copenhagen V.
Secretary: Dr. Folke Tudvad, Sundby Hospital, Copenhagen.
Place: Rigshospitalet, Children's Department, Copenhagen. Time: Monthly.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. E. Lorenz, Mozartgasse 14, Universitäts-Kinderklinik, Graz, Österreich.
Vice-President: Prof. K. Klinke, Moorenstr. 5, Kinderklinik d. med. Akademie.
Secretary: Prof. Dr. J. Jochims, Städt. Krankenhaus Süd, Kronsforder Allee 71/73, Lübeck.
President for 1959: Prof. A. Wiskott, München, Universitäts-Kinderklinik.
Place: München. Time: Aug. 31-Sept. 2, 1959.

Finnish Pediatric Association

President: Dr. Niilo Hallmann, 11 Stenbäckinkatu, Helsinki.
Vice-President: Dr. Bernhard Landtman, Unioninkatu 45B, Helsinki.
Secretary: Dr. Kalle Österlund, Hiihtäjäntie 6 B14, Helsinki-Herttoniemi.
Place: Helsinki. Time: Five to six times a year.

Greek Pediatric Society

President: Dr. Egle Inglessi, Marrommateon 29, Athens.
Vice-President: Dr. Nicas Zervos, Nikis St., Athens.
Secretary: Dr. Christos Kassimoe, Marni St. 4, Athens.
Place: Athens University. Time: Monthly.

Israel Pediatric Society

Chairman: Dr. B. Ostrowski, Beth Harofeh, 2 Wingate Ave., Haifa.
Secretary: Dr. E. Freundlich, Rambam Government Hospital, Haifa.
Place: Haifa. Time: September, 1960.

National Society of Child Health and Pediatrics of Turkey

President: Dr. Behçet Uz, Izmir.
Vice-President: Prof. S. S. Soysal, Istanbul.
Executive Secretary: Prof. I. Dogramaci, Research Institute of Child Health, Hacettepe Parki, Ankara.

Nederlandse Vereniging voor Kindergeneeskunde

President: Prof. Dr. W. K. Dicke, Wilhelmina Kinderziekenhuis, Nieuwe Gracht 137, Utrecht.
Honorary Secretary: Dr. H. Reerink, Sophia Kinderziekenhuis, Gordelweg 160, Rotterdam.
Place: Variable. Time: Three times a year.

New Zealand Paediatric Society

President: Dr. Alice M. Bush, 18 Symonds St., Auckland C. 1.
Vice-President: Dr. J. M. Watt.
Secretary: Dr. Leo Phillips, 34 Princes St., Auckland.
Place: Wellington. Time: September, 1959.

Norsk Pediatrisk Selskap

President: Dr. E. Eyvind Ek, Oslo City Health Department, Oslo.
Vice-President: Dr. Martin Seip, Pediatric Department, Rikshospitalet, Oslo.
Secretary: Dr. K. Harnes, Pediatric Department, Rikshospitalet, Oslo.
Place: Pediatric Department, Rikshospitalet, Oslo. Time: Six or seven meetings a year.

Paediatric Society of Victoria

President: Dr. J. H. Colebatch, 12 Collins St., Melbourne.
Vice-President: Dr. Murray Clarke, 12 Collins St., Melbourne.
Honorary Secretary: Dr. H. N. B. Wettenhall, 41 Spring St., Melbourne.
Place: Royal Children's Hospital. Time: Second Wednesday in each month.

Philippine Pediatric Society

President: Dr. Leon V. Pecoche, 1060 Zobel, Ermita.
Vice-President: Dr. Remedios G. Arellano, 125 Kanlaon, Quezon City.
Secretary: Dr. Emilia L. Palarca, North General Hospital, Manila.
Place: Physician's Club, Dewey Blvd., Manila. Time: Every two months; last Thursday of September, November, January, and March.

Royal Society of Medicine, Section of Paediatrics

President: Dr. Charles Pinkney, 73 Harley St., London W. 1.
Vice-Presidents: Drs. Vernon Braithwaite, D. V. Hubble, and A. Doyne.

Honorary Secretaries: Drs. H. H. Nixon, 12 Kemerton Rd., Beckenham, Kent, and Hugh Jolly, Yennadon House, Yelverton, So. Devon.
Place: 1 Wimpole St., London, W. 1. Time: Fourth Friday of each month from October to May.

SCHWEIZERISCHE GESELLSCHAFT FÜR PAEDIATRIE

President: Prof. W. Tobler, Brunnadernrain 11, Bern.
Vice-President: Prof. M. Jaccottet, Av. de Rumine, Lausanne.
Secretary: Dr. J. Haas, Westl. Alpenstrasse 3, Burddorf.

SCOTTISH PAEDIATRIC SOCIETY

President: Dr. Agnes Macgregor.
Secretary: Dr. R. G. Mitchell, Dept. of Child Health, Queen's College, Dundee.
Place: Glasgow, Edinburgh, Aberdeen, or Dundee. Time: Twice a year.

SOCIEDAD ARGENTINA DE PEDIATRÍA

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

SOCIEDAD BOLIVIANA DE PEDIATRÍA

President: Dr. Carlos Daza Meruvia, Casilla 2377, LaPaz.
Vice-President: Dr. Luis V. Sotelo, Casilla 1248, LaPaz.
Secretary: Dr. Cecilio Abela Deheza, Casilla 393, LaPaz.
Place: Hospital de la Cajade Seguro. Time: Every Saturday.

SOCIEDAD CHIHUAHUENESE DE PEDIATRÍA

President: Dr. Alfonso Riuz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

SOCIEDAD CHILENA DE PEDIATRÍA

President: Dr. Marco Maldonado, Esmeralda 678.
Vice-President: Dr. Ramón Montero, Esmeralda 678.
Secretary: Dr. Arturo Gallo, Esmeralda 678.
Place: Medical Society, Merced 565, Santiago. Time: Two times a month, Thursday.

SOCIEDAD COLOMBIANA DE PEDIATRÍA

President: Dr. Ernesto Plata-Rueda.
Vice-President: Dr. Carlos Albornoz-Medina
Secretary: Dr. Guillermo Correal Sanin.
Place: Sede de Sociedades Cientificas, Cra. 7, 31-46, Apt. 401. Time: Second Friday of each month.

SOCIEDAD CUBANA DE PEDIATRÍA (FILIAL CIENFUEGOS)

President: Dr. Rafael Viego Delgado.
Secretary: Dr. Ramón Azaret Morón, Santa Cruz No. 167, Cienfuegos, Cuba.
Place: Colegio Médico. Time: 9:00 p. m., Wednesdays, six times a year.

SOCIEDAD ECUATORIANA DE PEDIATRÍA

President: Dr. Aldo Muggia, P. O. Box 458, Quito, Ecuador.
Vice-President: Dr. Jorge Flores, Hospital Baca Ortiz, Quito, Ecuador.
Secretary: Dr. Nicolas Espinosa, Amazonas 743, Quito, Ecuador.
Treasurer: Dr. Dimas Burbano B.
Place: Hospital De Niños Baca Ortiz, Quito, Ecuador. Time: First Monday of month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month, April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DEL LITORAL

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

Sociedad de Pediatria del Valie del Cauca

President: Dr. Efrain Quevedo Velásquez.
Vice-President: Dr. Benjamín Rojas Pacheco.
Secretary: Dr. Uriel Estrada Calderon, Edificio Mericruz Apto. 401.
Time: First and third Thursday of each month.

Sociedad de Pediatría y del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Herando Barrios-Angulo.

Sociedad Uruguaya de Pediatría

President: Dr. Julio R. Marcos, Av. 8 de Octubre 2710, Montevideo.
Vice-President: Dr. José Alberto Praderi.
Secretary: Dr. Norma Curbelo Gamba, Enrique Muñoz 932, Montevideo.
Place: Av Agraciada 1464, piso 13, Montevideo. Time: First and third Wednesday of each month.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. Hernán Méndez Castellano, San Rafael de la Florida, Ave Los Claveles Qta., Mariela, Caracas.
Vice-President: Dr. Hernán Quintero Uzcátegui, Urb. Altamira, la. Ave., entre 9 y tranversales, Edo, Miranda.
Secretary: Dr. Eduardo Urdaneta, Cárcel a Monzón N° 104, Caracas.
Place: Medical College of Federal District. Time: Weekly.

Sociedad Yucateca de Pediatría

President: Dr. Humberto Perz Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

Sociedade Meneira de Pediatría

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

Sociedade de Pediatria da Bahia

President: Dr. Elysio Pereira de Atbayde.
Secretary: Dr. Eliezer Audiface.

Sociedade de Pediatria de Pernambuco

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

Sociedade Portuguesa de Pediatria

President: Prof. Carlos Salazar de Sousa, Avenida da Republica 64, Lisbon.
Vice-President: Dr. José dos Santos Bessa, Largo da Si Velha, Coimbra.
Secretary: Dr. Mario Cordeiro, Avenida do Restelo 17, Lisbon.
Place: Lisbon. Time: Once a month.

Sociedade de Puericultura e Pediatria do Maranbao

President: Dr. Ordorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

Societa Italiana di Pediatria

President: Prof. Giuseppe Caronia.
Vice-Presidents: Prof. Mario Cotellessa and Prof. Gaetano Salvioli.
Secretary: Prof. Rolando Bulgarelli.

Société Belge de Pédiatrie

Chairman: Dr. G. Helderweirt, 110 Ave. de Belgigue, Anvers.
Secretary-General: Dr. L. de Leener, 32 Ave. d'Auderghem, Bruxelles 4.
Treasurer: Dr. R. Capelle, Ave. Prince Baudouin 51, Bruxelles.

Société Francaise de Pédiatrie

President: Prof. Paul Rohmer, 6 Quai Foch, Strasbourg.
Vice-President: Prof. Raymond Turpin, 194 Avenue Victor Hugo, Paris (XVI).
Secretary: Prof. Maurice Lamy, 94 Rue de Varenne, Paris (VII).
Place: Hôpital des enfants-malades, 149 Rue de Sèvres, Paris (XV). Time: Third Tuesday of every month.

Société de Pédiatrie de Montréal

President: Dr. Paul Dagenais-Perusse, 301 Carre, St. Louis.
Vice-President: Dr. Jean Piette, 517 Cherrier.
Secretary: Dr. Guy Girardio, 4074 LaSalle Blvd.
Place: Variable. Time: Quarterly.

Société de Pédiatrie de Paris

President: Prof. Marcel Lelong, 197 Boulevard St.-Germain (VII).
Secretary: Prof. Maurice Lamy, 94 Rue de Varenne (VII).
Place: Hôpital des enfants-malades, 149 Rue de Sèvres (XV). Time: 4:00 p. m., third Thursday of each month.

Société de Pédiatrie de Québec

President: Dr. Antoine Larue, 1193 des Érables, Québec.
Vice-President: Dr. Antoine Bélanger, 38 Ave. Bégin Lévis, Québec.
Secretary: Dr. Maurice Richard, 1215 Ave. des Pins, Sillery.
Place: Québec. Time: First week of May and November.

Société Suisse de Pédiatrie

President: Prof. M. Jaccottet, Hôpital Cantonal, Lausanne.
Vice-President: Prof. Willy, Zurich.
Secretary: Dr. E. Juillard, Hôpital Cantonal, Lausanne.
Time: June.

South African Paediatric Association

President: Dr. B. Epstein, Medical Centre, Pretoria.
Vice-President: Prof. J. Davel, University of Pretoria, Pretoria.
Secretary: Dr. E. Fasser, 201 Medical Centre, 319 Pretorius St., Pretoria.

Swedish Pediatric Society

President: Prof. Bo Vahlquist, Pediatriska Kliniken, Akademiska Sjukhuset, Uppsala.
Vice-President: Dr. Orve Naglo, Hantoerkaregatan, Stockholm.
Secretary: Dr. Marcel d'Avignon, Karlavägen 40, Stockholm.
Place: Svenska Läkaresällskapet, Stockholm. Time: Second Friday, every month, except summer.

UNITED STATES

National

American Academy of Pediatrics

President: Dr. James C. Overall, 1924 Church St., Nashville 3, Tenn.
Vice-President: Dr. W. W. Belford, 420 Walnut St., San Diego 3, Calif.
Executive Secretary: Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.
Place: Palmer House, Chicago. Time: Annual Meeting, Oct. 5-8, 1959.

American Medical Association, Section on Pediatrics

Chairman: Dr. Wyman C. Cole, 3001 W. Grand Blvd., Detroit 2.
Vice-President: E. Revere Cole, 2901 Capital Ave., Sacramento, Calif.
Secretary: Dr. Arild Hansen, University of Texas Medical Branch, Galveston, Texas.

American Pediatric Society

President: Dr. Joseph Stokes Jr., 1740 Bainbridge St., Philadelphia 46.
Vice-President: Dr. W. L. Bradford, 260 Crittenden Blvd., Rochester 20, N. Y.
Secretary: Dr. Aims C. McGuinness, 2800 Quebec St., N. W., Washington 8, D. C.
Place: The Inn, Buck Hill Falls, Pa.

Society for Pediatric Research

President: Dr. Sydney S. Gellis, 818 Harrison Ave., Boston 18.
Vice-President: Dr. Margaret Smith, 550 1st Ave., New York 16.
Secretary: Dr. Clark West, Children's Hospital, Cincinnati 29.
Place: The Inn, Buck Hill Falls, Pa.

Sectional

Intermountain Pediatric Society

President: Dr. Wesley H. Anderson, 39 Virginia Professional Building, Ogden, Utah.
Secretary: Dr. J. Bruce Balken, 2955 Harrison Blvd., Ogden, Utah.

New England Pediatric Society

President: Dr. Sydney Gellis, Boston City Hospital, Boston.
Vice-President: Dr. David Clement, 240 Bradley St., New Haven, Conn.
Secretary: Dr. Harry Shwachman, Children's Hospital, Boston.
Place: Three meetings in Boston; spring meeting, variable. Time: Four meetings per year.

North Pacific Pediatric Society

President: Dr. Scott Goodnight, 1440 S. W. Taylor, Portland 1.
Vice-President: Dr. Vernon Spickard, 1305 4th Ave., Seattle.
Secretary: Dr. Arthur May, 1440 S. W. Taylor Ave., Portland 1.
Place: Victoria, B. C. Time: September.

Northwestern Pediatric Society

President: Dr. John D. Bailey, Box 849, Rapid City, S. D.
Vice-President: Dr. H. M. Medovy, University of Manitoba, Winnipeg, Canada.
Secretary-Treasurer: Dr. John C. O'Brien, 868 Lowry Medical Arts Building, St. Paul.

Rocky Mountain Pediatric Society

President: Dr. Alfred Hicks II, 1592 Madison St., Denver.
Vice-President: Dr. James Watson, Colorado Springs, Colo.
Secretary: Dr. Frank J. Cozzetto, 2401 E. 6th Ave., Denver 6.
Place: Announced before each meeting. Time: Quarterly.

Southwestern Pediatric Society

President: Dr. Wendell Redfern, 720 N. Brand Blvd., Glendale, Calif.
Vice-President: Dr. Chester Tancredi, 411 Thorn St., San Diego, Calif.
Secretary: Dr. Robert Shirley, 11633 San Vicente Blvd., Los Angeles 49.
Place: University Club of Los Angeles. Time: Second Wednesday, September, November, January, March, and June.

Western Society for Pediatric Research

President: Dr. James F. Bosma, 1940 S. 2d East, Salt Lake City.
Vice-President: Dr. William Deamer, Dept. of Pediatrics, University of California, San Francisco.
Secretary: Dr. Robert H. Alway, Stanford School of Medicine, San Francisco.
Place: Salt Lake City.

State

Academy of Pediatrics, Indiana Chapter

President: Dr. William M. Browning, 3740 Central Ave., Indianapolis 5.

Arizona Pediatric Society

President: Dr. Hiram Cochran, 116 N. Tucson Blvd., Tucson.
Secretary: Dr. Sidney R. Kemberling, 116 N. Tucson Blvd., Tucson.
Place: Chandler. Time: Yearly at State A. M. A. Meeting.

California Medical Association, Section on Pediatrics

Chairman: Dr. Percy H. Jennings Jr., 1650 Walnut St. Berkeley 9.
Secretary: Dr. Gordon L. Richardson, 10711 Riverside Drive, N. Hollywood.

District of Columbia Medical Society, Pediatric Section

President: Dr. Richard Todd.
Secretary: Dr. Sanford Leikin, Childrens Hospital, Washington, D. C.

Florida State Pediatric Society

President: Dr. Burns A. Dobbins, 120 E. Broward Blvd., Fort Lauderdale.
Vice-President: Dr. Harry M. Edwards, 1139 S. Orange St., Ocala.
Secretary: Dr. Camillus S. L'Engle, 1186 Edgewood Ave., Jacksonville.

Georgia Pediatric Society

President: Dr. Edwin R. Watson, 745 Pine St., Macon.
Vice-President: Dr. Richard L. Schley Jr., 303 11th St., Columbus.
Secretary-Treasurer: Dr. LeRoy Antrobus, 3130 Maple Dr., N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Abe S. Brown, 58 Central Ave., Waterbury.
Secretary: Dr. Thomas Monagan, 195 Grove St., Waterbury.

Illinois State Medical Society, Section on Pediatrics

President: Dr. Lawrence Breslow, 2424 W. Peterson, Chicago 45.
Secretary: Dr. Homer Weir, 1429 Myott Ave., Rockford.
Place: Chicago.

Iowa Pediatric Society

President: Dr. Guido J. Sartor, Mason City.
Vice-President: Dr. John C. McQueen, Pediatric Department, State University of Iowa, Iowa City.
Secretary: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines 11.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting; fall meeting in September at University Hospital, Iowa City.

Kansas State Pediatric Society

President: Dr. Hilbert P. Jubelt, 1200 Fremont St., Manhattan.
Vice-President: Dr. Thomas C. Hurst, 405 K. F. H. Building, Wichita.
Secretary: Dr. William H. Crouch, 306 Medical Arts Building, Topeka.
Place: Emporia. Time: 9:30 a. m., first Saturday after Labor Day.

Kentucky Pediatric Society

President: Dr. Robert McLeod, Somerset.
Vice-President: Dr. Robert L. Rice, Richmond.
Secretary: Dr. Leslie W. Langley Jr., Somerset.
Place: Somerset. Time: April.

Louisiana State Pediatric Society

President: Dr. Bertha Wexler, New Orleans.
President-Elect: Dr. Thomas E. Strain Sr., Shreveport.
Secretary: Dr. Dorothy J. York, 2902 Napoleon Ave., New Orleans.
Place: New Orleans.

Michigan State Medical Society, Pediatric Section

President: Dr. Harry A. Towsley, University Hospital, 1313 Ann St., Ann Arbor.
Secretary: Dr. Charles Frank Payton, 611 S. Washington, Royal Oak.

Montana Pediatric Society

President: Dr. John Halseth, Great Falls Clinic, Great Falls.
Secretary: Dr. George Barmeyer, Western Montana Clinic, Missoula.
Place: Helena.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Frank A. Stewart, 2133 Winthrop Rd., Lincoln.
Vice-President: Dr. A. J. Lombardo, 401 Aquila Court, Omaha.
Secretary: Dr. F. Marshall Zahller, 5517 Military Ave., Omaha.
Place: Children's Hospital, Omaha, or announced. Time: Third Thursday of month.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. Robert F. Wilson, 113 Locust St., Dover.
Secretary: Dr. Arthur E. Laidlaw, Keene Clinic, Keene.
Place: Variable. Time: Variable.

NEW MEXICO PEDIATRIC SOCIETY

President: Dr. Stuart W. Adler, 717 Encino N. E. Albuquerque.
Vice-President: Dr. Guy E. Radar, 4200 Silver S. E., Albuquerque.
Secretary: Dr. Eleanor L. Adler, 717 Encino N. E., Albuquerque.
Place: Variable. Time: Four times a year.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Leroy J. Butler, Winston-Salem.
President-Elect: Dr. Thomas A. Hensen, Greensboro.
Secretary-Treasurer: Dr. John F. Lynch Jr., Greensboro.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Fred Adams, 157 Pine St., Spartanburg.
Vice-President: Dr. C. Guy Castle Jr., 1417 Gregg St., Columbia.
Secretary: Dr. Charles Zemp, 1105 Lyttleton St., Camden.
Place: Columbia and Myrtle Beach. Time: September and May of each year.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Gilbert Levy, 188 S. Bellevue, Memphis.
Vice-President: Dr. Jack Chesney, Knoxville.
Secretary: Dr. Robert G. Jordan Jr., 848 Adams, Memphis.
Place: Memphis.

TEXAS PEDIATRIC SOCIETY

President: Dr. Bruce A. Knickerbocker, 3403 Hall St., Dallas 4.
Secretary: Dr. James N. Walker, 5216 W. Freeway, Fort Worth 7.
Place: Houston. Time: October, 1959.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Robert H. Cox Jr., Allied Medical Arts Building, Lynchburg.
Vice-President: Dr. O. Watts Booth, 87 29th St., Newport News.
Secretary: Dr. John T. Walke, 302 Washington, S. W., Roanoke.

WISCONSIN STATE MEDICAL SOCIETY, SECTION OF PEDIATRICS

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

AKRON PEDIATRIC SOCIETY

President: Dr. Edward A. Sawan, 111 W. State St.
Vice-President: Dr. John Norman, 513 W. Market St.
Secretary: Dr. Frederick Fiedorek, 2695 N. Haven Blvd., Cuyahoga Falls, Ohio.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

President: Dr. Melchijah Spragins, 102 Alleghany Ave., Towson 4, Md.
Vice-President: Dr. Harry H. Gordon, Sinai Hospital of Baltimore, Inc., Monument St. and Rutland Ave. (5).
Secretary: Dr. B. M. Debuskey, 2501 W. Belvedere Ave.
Place: 1211 Cathedral St. Time: Second Tuesday in November, January, and March.

Baton Rouge Pediatric Society

President: Dr. John Ray Powers, 3347 Government St.
Vice-President: Dr. David S. Miller, 3642 Claycut Rd.
Secretary: Dr. Francis M. Harris Jr., 1401 N. Foster Dr.
Time: Quarterly as called.

Bronx Pediatric Society

President: Dr. Archie Cohen, 2280 Grand Ave.
Vice-President: Dr. Arthur A. Goldfarb, 1150 Grand Concourse.
Secretary: Dr. Louis Penn, 1505 Grand Concourse.
Place: Morrisania Hospital. Time: Second Wednesday of each month.

Brooklyn Academy of Pediatrics

President: Dr. Joseph Pincus, 881 Washington Ave. (25).
Vice-President: Dr. Morris Steiner, 456 E. 19th St. (26).
Secretary: Dr. Saul Starr, 1822 Ave. H. (30).
Place: Hotel Granada. Time: Fourth Wednesday of each month.

Buffalo Pediatric Society

President: Dr. Norman C. Bender, 227 Colvin Ave.
Vice-President: Dr. Thomas S. Bumbalo, 354 Lincoln Parkway.
Secretary: Dr. Lois J. Plummer, 131 Linwood Ave.
Place: Alternating Buffalo Children's Hospital and Edward J. Meyer Memorial Hospital.
Time: Fall, winter, and spring and on call.

Central Illinois Pediatric Society

President: Dr. Paul P. Pierce, 1900 Brown St., Alton.
Vice-President: Dr. J. Keller Mack, 614 S. Seventh St., Springfield.
Secretary-Treasurer: Dr. Richard E. Dukes, Carle Hospital Clinic, Urbana.
Place: Rotated among cities in central Illinois. Time: Spring and Fall.

Central New York Pediatric Club

President: Dr. George R. Murphy, Elmira.
Vice-President: Dr. Herbert Soule Jr., Rochester.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester 7.
Place: Variable. Time: Spring and fall.

Central Ohio Pediatric Society

President: Dr. William Newton, Children's Hospital, Columbus.
Secretary: Dr. Robert Batterson, 350 E. Broad St., Columbus.
Place: Variable. Time: Third Wednesday, September, November, January, March, May.

Chicago Pediatric Society

President: Dr. Noel G. Shaw, 2901 W. Central St., Evanston, Ill.
Vice-President: Dr. Raymond R. Grissom, 715 Lake St., Oak Park, Ill.
Secretary: Dr. James A. Conner, 101 S. Garfield, Hinsdale, Ill.
Place: Children's Memorial Hospital. Time: 8:30 p. m., third Tuesday in each month, October to May.

Cincinnati Pediatric Society

President: Dr. Harold A. Cassady, 2728 Erie Ave.
Vice-President: Dr. Carl V. Ochs, 2727 Madison Rd.
Secretary: Dr. Carl A. Koch, 3511 Glenmore Ave.
Place: Children's Hospital. Time: Quarterly.

Corpus Christi Pediatric Society

President: Dr. Joseph Oshman, 1010 Ohio.
Vice-President: Dr. Mary McCaskey, 1001 Louisiana.
Secretary: Dr. Helen Woods, 2526 Morgan.
Time: Fourth Wednesday, every two months.

Dallas Pediatric Society

President: Dr. Hugh W. S. Powers Jr., 8215 Westchester.
Secretary-Treasurer: Dr. Melvin G. Russell, 936 N. Edgefield.
Place: Children's Medical Center. Time: 6:30 p. m., first Thursday in each month.

Des Moines Pediatric Society

President: Dr. Charles L. Burr, 5701 Hickman Ave.
Vice-President: Dr. James E. Dyson, 3200 University Ave.
Secretary-Treasurer: Dr. Glen E. Nielsen, 3009 Ingersoll Ave.
Place: Des Moines Golf and Country Club. Time: Fourth Tuesday of each month, October to May.

Detroit Pediatric Society

President: Dr. Douglas Wake, 1307 S. Washington, Royal Oak, Mich.
Vice-President: Dr. Irving E. Burton, 15041 E. Seven Mile Rd.
Secretary: Dr. Carl Witus, 15041 E. Seven Mile Rd.
Place: Variable. Time: First Wednesday of each month.

Fort Worth Pediatric Society

President: Dr. Harry Womack, 1424 W. Peter Smith.
Secretary: Dr. Blanche O. Terrell, 1425 Pennsylvania Ave.
Place: Variable. Time: Fourth Friday of each month.

Hinterland Pediatric Society

President: Dr. Edward Zeman, 3616 Main St., Riverside, Calif.
Vice-President: Dr. George A. Chalfant, 1086 San Bernardino Rd., Upland, Calif.
Secretary: Dr. John Morris, 1236 N. Waterman Ave., San Bernardino, Calif.
Place: Alternating San Bernardino, Riverside, and Pomona. Time: Fourth Tuesday of February, May, September, and October.

Honolulu Pediatric Society

President: Dr. Duke Cho Choy, Medical Arts Bldg.
Secretary-Treasurer: Dr. Calvin Sia, 1305 Kalakaua Ave.
Corresponding Secretary: Dr. Frances Nakamura, 1481 S. King St.
Place: Members' homes. Time: 6:30 p. m., third Thursday of each month.

Houston Pediatric Society

President: Dr. Robert Lomas, 1731 Sunset Blvd.
Vice-President: Dr. Juanita Hart, 306 S. 7th St., Bellaire, Texas.
Secretary: Dr. Hubert L. Ried, 2229 Dorrington Blvd.
Treasurer: Dr. Gerald Y. George.
Place: River Oaks Country Club. Time: 6:30 p. m., fourth Tuesday in January, March, May, July, September, and November.

Kansas City Southwest Pediatric Society

President: Dr. George W. Wise, Plaza Parkway Bldg., Kansas City, Mo.
Vice-President: Dr. Theodore Edwards, 329 E. Armour, N. Kansas City, Mo.
Secretary: Gerald Hughes, 6509 Prospect, Kansas City, Mo.
Place: Country Club. Time: Quarterly, on call.

Long Beach Pediatric Society

President: Dr. James Fowler, 2240 Pacific Ave.
Vice-President: Dr. Milton Katz, 1868 Pacific Ave.
Secretary: Dr. David M. Rozran, 911 E. San Antonio Dr.
Place: University Club, 1150 E. Ocean Blvd. Time: First Tuesday of each month.

Los Angeles Pediatric Society

President: Dr. Wendell M. Redfern, 125 E. Glenoaks, Glendale.
Vice-President: Dr. Morris J. Naiditch, 239 S. La Cienega Blvd., Beverly Hills.
Secretary-Treasurer: Dr. Neil N. Litman, 5830 Overhill Dr. (43).
Place: 1925 Wilshire Blvd. Time: Second Thursday in January, March, May, October.

Louisville Pediatric Society

President: Dr. Edwin Paul Scott, 3610 Lexington Rd.
Vice-President: Dr. Martin J. Harris, Francis Building, 4th & Chestnut Sts.
Secretary: Dr. Paul Patrick Hess, Floyd County Bank Building, New Albany, Ind.
Place: Variable. Time: Four times a year.

MEDICAL SOCIETY OF THE COUNTY OF KINGS, BROOKLYN PEDIATRIC SECTION

President: Dr. David Dragutsky, 1466 49th St.
Vice-President: Dr. Abraham Gilner, 303 Beverly Rd., Brooklyn 18.
Secretary: Dr. Saul Starr, 1822 Ave., H.
Place: King's County Medical Society Building. Time: 9:00 p. m., fourth Monday of October, November, January, March, and April.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION OF PEDIATRICS

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Vice-President: Dr. W. A. Howard, 1517 30th St. N. W., Washington, D. C.
Secretary: Dr. John E. Cassidy, 9911 Old Georgetown Rd., Bethesda, Md.
Place: Medical Society Building. Time: On call.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. M. Blake Arnoult, 4720 Poplar Ave.
Vice-President: Dr. Kinsey M. Buck, 1193 Madison Ave.
Secretary: Dr. William W. Mason, 3314 Poplar Ave.
Place: Memphis Country Club. Time: Second Tuesday of March, June, September, and December.

MIAMI PEDIATRIC SOCIETY

President: Dr. Howard A. Engle, 975 Arthur Godfrey Rd.
Secretary-Treasurer: Dr. Charles Rosenfeld, 1500 Coral Way.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. J. C. Peterson, 721 N. 17th St.
Vice-President: Dr. Ted Buszkiewicz, 3333 S. 27th St.
Secretary: Dr. Leonard Gorenstein, 945 N. 12th St.
Place: University Club. Time: Second Wednesday of alternate months.

MOBILE PEDIATRIC SOCIETY

President: Dr. Robert O. Harris III, 2 N. Florida St.
Secretary: Dr. James W. Coker Jr., 1367 Government St.
Place: Variable. Time: Quarterly.

MONTGOMERY COUNTY PEDIATRIC SOCIETY

President: Dr. C. E. Robert Parker, 335 S. Ripley St., Montgomery, Ala.
Vice-President: Dr. William R. Britton, 133 S. Union, Montgomery.
Secretary: Dr. William B. Brock, 1709 Pipe St., Montgomery.
Place: Montgomery. Time: Quarterly.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. Harry M. Estes, 1924 Hayes St.
Secretary: Dr. Ray L. Dubuisson, Formosa Building, Hillsboro Dr.
Place: Members' homes. Time: Third Thursday of each month.

NASSAU PEDIATRIC SOCIETY

President: Dr. Selma Buchbinder, 295 Harvard Ave., Rockville Centre, N. Y.
Vice-President: Dr. James Dick, 230 Hilton Ave., Hempstead, N. Y.
Secretary-Treasurer: Dr. David Posner, 98 Wolcott Rd., Levittown, N. Y.
Place: Felice's Restaurant, Westbury, Long Island. Time: Second Monday in February, April, June, October, and December.

NEW ORLEANS PEDIATRIC SOCIETY

President: Dr. Norman Robinson, 1520 Louisiana Ave.
Vice-President: Dr. Richard P. Vieth, 3411 Coliseum St.
Secretary-Treasurer: Dr. Thomas Furlowe, 2110 Foy St.
Place: Variable. Time: Six times a year.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. Benjamin Kramer, 60 Plaza St., Brooklyn.
Secretary: Dr. Henry L. Barnett, 535 East 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St., New York.
Time: 8:30 p. m., every second Thursday of October through May.

NORTHERN OHIO PEDIATRIC SOCIETY

President: Dr. Leon H. Dembo, 10465 Carnegie Ave., Cleveland 6.
President-Elect: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland 6.
Secretary: Dr. Hugh Leslie Jr., 5867 Mayfield Rd., Cleveland 24.
Place: Designated individually for each meeting. Time: Four times yearly.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Jerome D. Shaffer, 1200 North Walker.
Secretary: Dr. Eric B. Meador, 2548 N. W. 23d.
Place: Variable. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Fred Harvie, Hospital of University of Pennsylvania.
Vice-President: Dr. Robert H. High, St. Christophers Hospital for Children.
Secretary: Dr. Charles Kennedy, Children's Hospital of Philadelphia.
Place: College of Physicians. Time: Second Tuesday of each month, October to May.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Robert Macdonald, 448 Brownsville Rd. (10).
Vice-President: Dr. Bernard I. Michaels, 3500 5th Ave. (13).
Secretary: Dr. James Reilly, 2331 Laketon Rd. (21).
Place: Variable. Time: January, March, May, September, November.

QUEENS PEDIATRIC SOCIETY

President: Dr. Benjamin Goldsmith, 4027 Murray St., Flushing 54, N. Y.
Vice-President: Dr. Fred Castrovinci, 3357 75th St., Jackson Heights 72, N. Y.
Secretary: Dr. Emanuel Fletcher, 14010 Franklin Ave., Flushing 55, N. Y.
Place: Seminole Club. Time: Second Tuesday of February, April, October, and December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Lillian C. Lindemann, 4708 Cary St. Rd.
Vice-President: Dr. Robert Hoffman, 5311 Patterson Ave.
Secretary: Dr. Martin A. Hoffman, West End Medical Center, Three Chopt and Kensington Ave.
Place: Variable. Time: Third Thursday of the month, 8:30 p. m.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Jackson K. Eto, 6500 Chippwa.
Vice-President: Dr. Leo F. Gowen, 337 W. Lockwood.
Secretary: Dr. James L. Donahoe, 950 Francis Place, Clayton 5, Mo.
Place: Park Plaza Hotel. Time: Quarterly.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Jerry Newton, 302 Croydon.
Vice-President: Dr. David S. Howard, 4119 Fredericksburg Rd.
Secretary: Dr. William B. Brendel, 111 Gen. Kreuger.
Place: Variable. Time: Second Tuesday of each month.

SANTA BARBARA PEDIATRIC SOCIETY

President: Dr. Louis Needles, County Health Department.
Secretary: Dr. Newton Wayland, 1515 State St.
Place: Variable. Time: On call.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Jack M. Doctor, 728 Broadway.
Secretary: Dr. John R. Hartmann, 4575 Sand Point Way.
Treasurer: Dr. William Warmington, 4115 University Way.
Place: College Club. Time: Third Friday of each month.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. James W. Skinner, 612 Elm St., St. Joseph, Mich.
Vice-President: Dr. David Dickinson, University Hospital, 540 Rock Creek Dr., Ann Arbor.
Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Department of Pediatrics, Ann Arbor.
Place: University Hospital, Ann Arbor. Time: Spring.

WACO PEDIATRIC SOCIETY

President: Dr. Charles Shellenberger, 2524 Washington Ave.
Secretary: Dr. Charles E. Gamble, 2524 Washington Ave.
Place: Children's Clinic. Time: Last Tuesday of each month.

WESTCHESTER COUNTY ACADEMY OF MEDICINE, PEDIATRIC SECTION

President: Dr. A. H. Hardy, 145 Corliss Ave., Pelham, N. Y.
Secretary: Dr. Irving Nelson, 150 E. Hartsdale Ave., Hartsdale, N. Y.
Place: Pforscheimer Memorial Building, Harrison, N. Y.

WESTERN MICHIGAN PEDIATRICS SOCIETY

President: Dr. John W. Thompson, 833 Lake Drive, S. E., Grand Rapids.
Vice-President: Dr. Ethon L. Stone. 721 17th St., Jackson.
Secretary: Dr. Donald C. Johns, 655 Broadview S. E., Grand Rapids.
Place: Grand Rapids in November and March. Other west Michigan cities in September and June.

WICHITA PEDIATRIC SOCIETY

President: Dr. William F. McGuire.
Secretary: Dr. Katherine Pennington, Sedgwick County Medical Society, Schwiter Building, Wichita, Kan.
Place: Homes of members. Time: 8:30 p. m., first Thursday, October through May.

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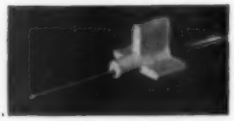

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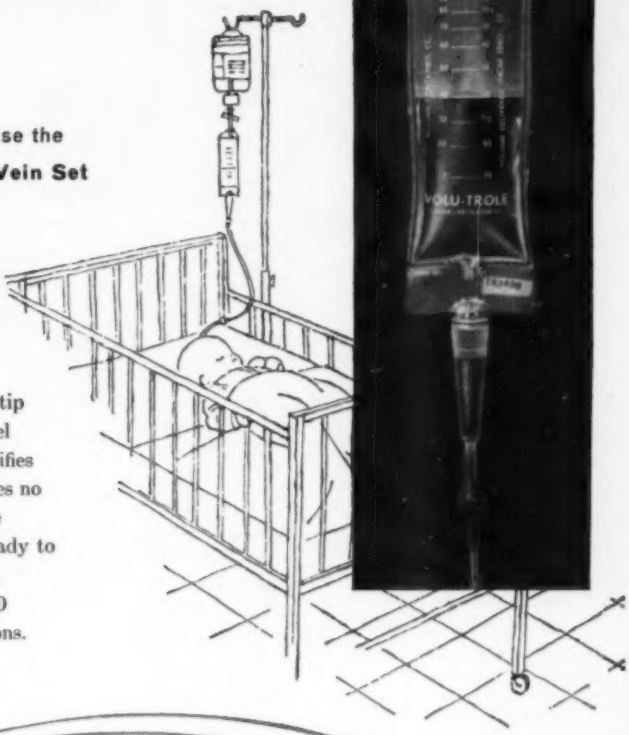

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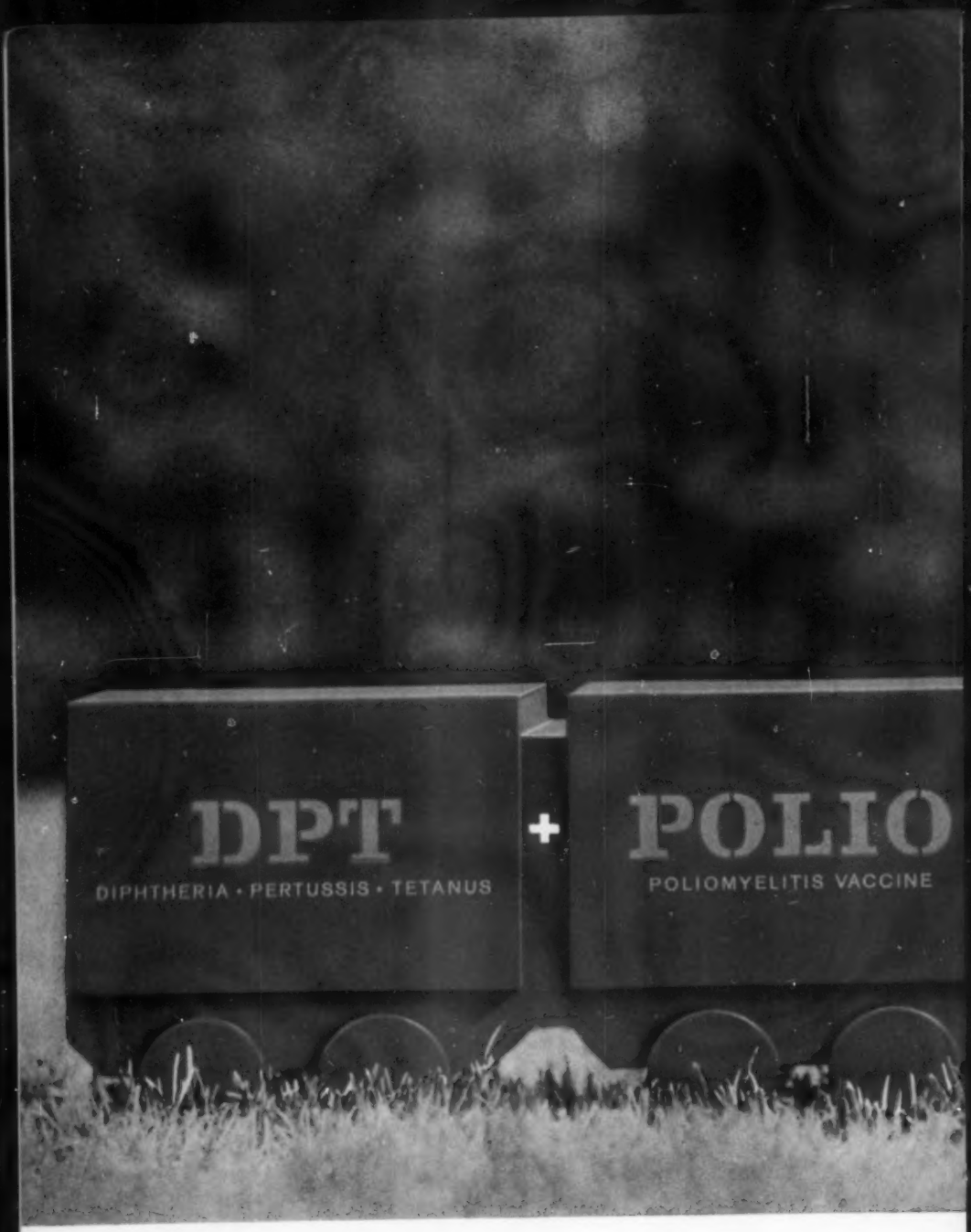

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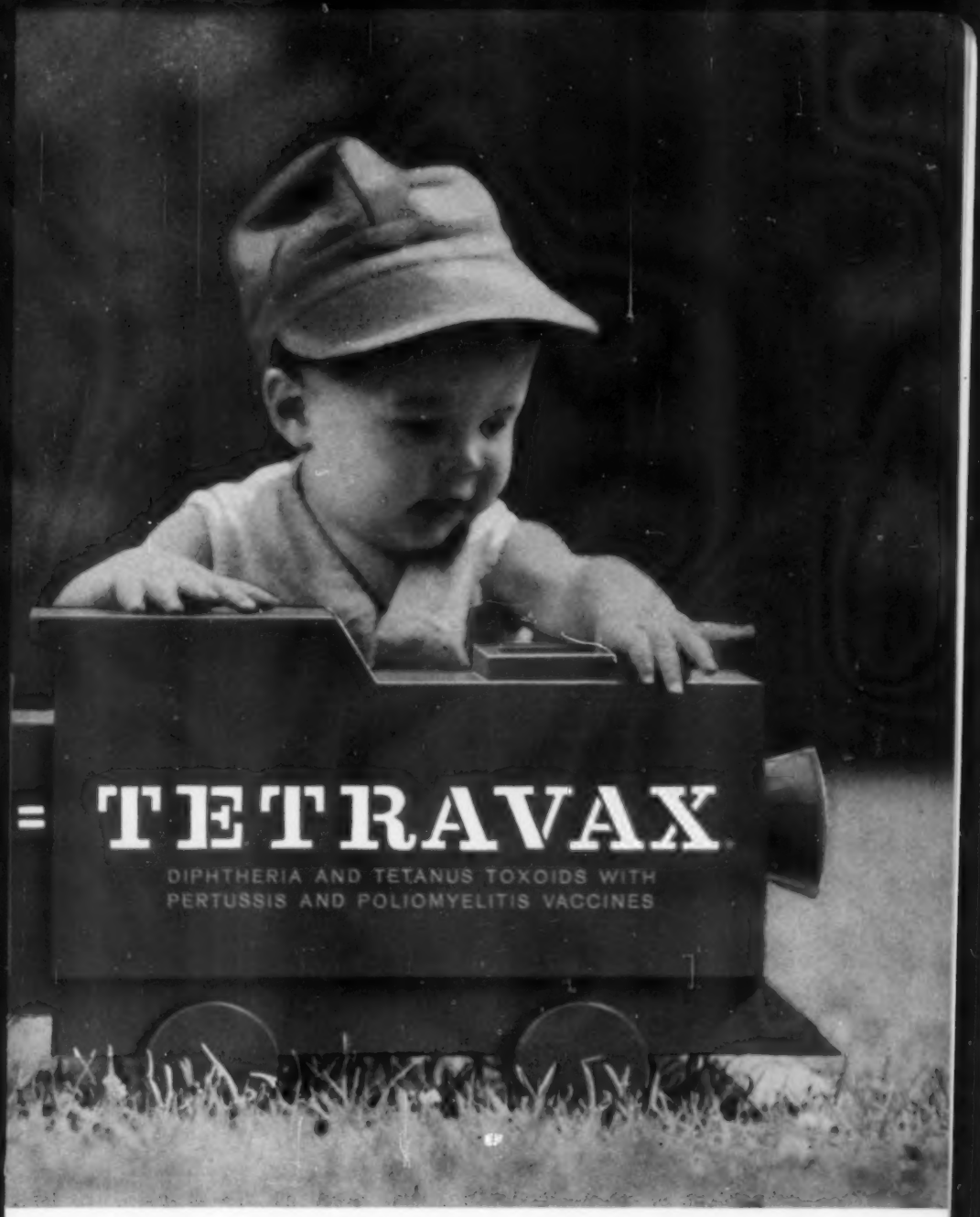

now immunization is possible against more *diseases — with* fewer *injections*

Dosage: 1 cc. *Supplied:* 9 cc. vials in *clear plastic* cartons. Package circular and material in vial can be examined without damaging carton. Expiration date is on vial for checking even if carton is discarded.

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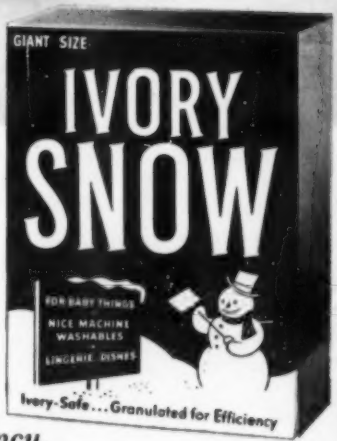

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Now for the first time

These Two Highly Effective Anti-Diarrheal Agents In One Convenient, Delicious Dosage Form For Infants and Children

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Neomycin Sulfate
for rapid and prolonged bacterial control.

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for prompt control of hyperperistalsis and intestinal discomfort.

Excellent results were obtained with PAREMYCIN Elixir in a group of 25 infants and children 6 months to 15 years of age with infectious diarrhea. "Symptomatic improvement in almost all cases occurred rapidly within 12 hours after initiation of treatment."[1]

NON-BULKY · EFFECTIVE IN SMALL DOSES · NON-CHALKY · UNSURPASSED PALATABILITY

DOSAGE: INFANTS (under two years of age) — ½ to 1 teaspoonful four times daily or as directed by physician. CHILDREN (over two years of age) — 1 to 2 teaspoonfuls four times daily or as directed by physician.

SUPPLY: Bottles of 6 and 3 fl. oz.

FOR INFANTS

℞ Paremycin Elixir
Sig: ℥ss q.i.d.

FOR CHILDREN

℞ Paremycin Elixir
Sig: ℥ i q.i.d.

1. Schneider, A. J. (Seattle, Wash.): Personal Communication, 1958

NOTE: As with any neomycin preparation, prolonged administration and high dosage levels should be avoided in view of possible systemic effects; do not administer in the presence of kidney damage.

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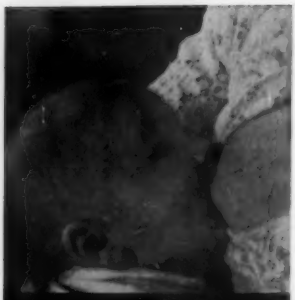

a new study of basic standards in infant feeding

DURATION, CONTINUITY, METHOD

Nitrogen retentions of infants fed breast milk or Similac were compared in the Metabolism Ward of the University Hospital at Iowa City – a homelike yet controlled environment. No solid foods were fed. Three-day balance studies were carried out on each infant approximately every 2 weeks for 6 months.

STANDARDS IN INFANT FEEDING

basis: BREAST MILK

The initial phase of investigation,[1,2] based on the primacy of breast milk as a reference standard in infant feeding,[3] was conducted to provide more detailed and sustained metabolic data than had previously been attempted. The authors derive from these data standard reference curves for nitrogen retention, as found in normal breast-fed infants.

comparison: SIMILAC®

The results with Similac showed progress in growth along normal curves. Nitrogen retentions occurred as with breast milk, in proportions relative to protein intake.[4] By the detailed metabolic criteria of the study, as by the clinical criteria of pediatric practice, Similac stands as a feeding closely comparable to breast milk.

SIMILAC SUPPLIES INFANT'S PROTEIN REQUIREMENT

"It is therefore concluded, as judged by these criteria, that the infant's requirement of protein from cow's milk is no greater than that supplied by ad libitum feeding of Formula S."[4]

References: 1. Fomon, S. J., and May, C. D.: Pediatrics *22*:101 (July) 1958. 2. Fomon, S. J.; Thomas, L. N., and May, C. D.: Pediatrics *22*:935 (Nov.) 1958. 3. May, C. D.: Pediatrics *23*:384 (Feb.) 1959. 4. Fomon, S. J., and May, C. D.: Pediatrics *22*:1134 (Dec.) 1958.

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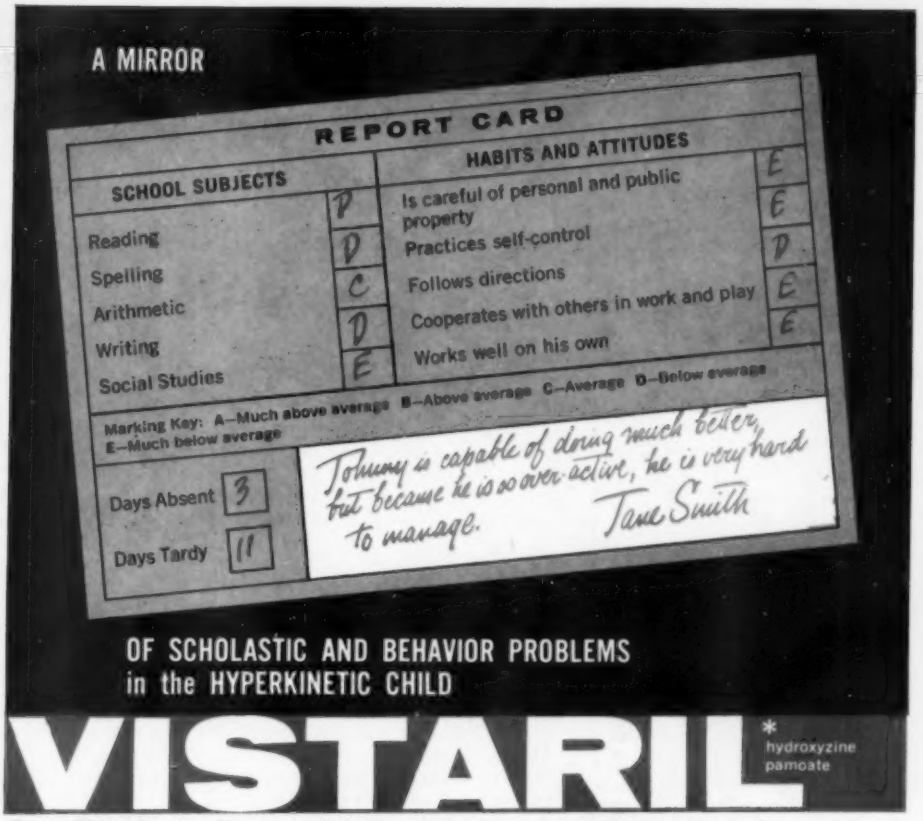
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SCHOOL SUBJECTS
Reading D
Spelling D
Arithmetic C
Writing D
Social Studies E
HABITS AND ATTITUDES
Is careful of personal and public property E
Practices self-control E
Follows directions D
Cooperates with others in work and play E
Works well on his own E
Marking Key: A—Much above average B—Above average C—Average D—Below average E—Much below average
Days Absent 3
Days Tardy 11
Tommy is capable of doing much better, but because he is so over-active, he is very hard to manage.
Jane Smith
OF SCHOLASTIC AND BEHAVIOR PROBLEMS
in the HYPERKINETIC CHILD
VISTARIL*
hydroxyzine pamoate

An effective adjuvant in the treatment of hyperkinesis

DEPENDABLE PSYCHOTHERAPEUTIC POTENCY exerts a calming effect on the hyperactive, impulsive, destructive, aggressive, and difficult-to-manage traits of the hyperkinetic child.

"It is especially valuable in helping to calm the so-called 'hyperkinetic' child who seems to be on a constant merry-go-round."[1] *"This drug lessens tensions, relieves symptoms of disturbed autonomic function and calms hyperkinetic behavior."*[2]

FREEDOM FROM MENTAL STAGNATION especially significant in the school child.

"The relative freedom from side effects makes hydroxyzine quite valuable for anxious children and hyperkinetic children, especially those attending school, in whom drug-induced psychic impairment is undesirable."[3]

RECOMMENDED ORAL DOSAGE IN PEDIATRICS: under 6 years—50 mg. daily in divided doses; 6 years and over—50-100 mg. daily in divided doses.

SUPPLY: Vistaril Capsules—25 mg., 50 mg., 100 mg.; Vistaril Parenteral Solution—10 cc. vials and 2 cc. Steraject® Cartridges, each cc. containing 25 mg. hydroxyzine (as the HCl).

REFERENCES: 1. Eisenberg, B. C.: Clinical Medicine *5*:897-904 (July) 1958. 2. Ayd, F. J., Jr.: Med. Arts and Sciences *2*:37, 1957. 3. Ayd, F. J., Jr.: New York State J. *57*:10 (May) 1957.

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Leads all other Whole-Grain Cereals in Quantity *and* Quality of Protein

The quality of protein is graded by several criteria of which the most frequently used are: total protein value* and protein efficiency ratio.** Independently published data[1] reveal that oatmeal excels on both counts:

	Total Protein Value	Protein Efficiency Ratio
Oatmeal	165	2.2
Whole wheat	140	1.5
Barley	87	1.8
Whole corn	84	1.2
Rice	57	1.9

Quantitatively, the customary oatmeal-with-milk dish (¾ cup cooked oatmeal and 4 fluid ounces milk) provides 9 grams of protein, more than that provided by any other whole-grain cereal with milk.

In addition to its qualitative and quantitative superiority in protein, oatmeal-and-milk supplies significant amounts of B vitamins and minerals to complement the excellent nutritive balance between protein, fat and carbohydrate.

Just as important to the physician who prescribes a cereal food is oatmeal's delicious nut-like flavor, its ease of digestion, and the ready availability of its contained nutrients. Whether it be for an infant's first solid feeding, for the geriatric patient, or in many other situations, oatmeal makes a real contribution to the day's nutritional needs.

Nutrition studies of The Quaker Oats Company Research Laboratories assure that Quaker Oats and Mother's Oats, the two brands of oatmeal marketed by The Quaker Oats Company, are practically identical with natural whole-grain oats in composition and in nutritive values. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

IN PEDIATRIC NUTRITION, oatmeal, with its easy digestibility and assimilation, and its wealth of essential nutrients, merits recommendation among the first solid foods as soon as spoon-feeding can be instituted.

*Total protein value is determined by multiplying biologic value x digestibility x per cent nitrogen. **Protein efficiency ratio is the efficiency with which an experimental animal utilizes each gram protein consumed.

1. Rand, N. T. and Collins, V. K.: Food Technology *12*:585 (Nov.) 1958.

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LOWILA® CAKE

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"Demerol as an analgesic lends itself favorably to pediatric practice . . ."[1]

For severe gastrointestinal colic, "...I now use when necessary, with highly satisfactory results, Elixir of Demerol."[2]

Usual dose:
1 mg. (2 drops) to 1.5 mg. (3 drops) per Kg. (2.2 lb.) of body weight.

Each teaspoon (5 cc.) of Elixir Demerol = 50 mg. Demerol HCl
Each cc. (20 drops) of Elixir Demerol = 10 mg. Demerol HCl
Each drop of Elixir Demerol = 0.5 mg. Demerol HCl

Supplied: Elixir Demerol, 50 mg. per teaspoon (5 cc.), bottles of 16 fl. oz.
Subject to regulations of the Federal Bureau of Narcotics.

1. Junkin, C. I.: *Canad. Anaesthetists' Soc. J.* 3:208, July, 1956.
2. Glaser, Jerome: *J. M. A. Georgia* 45:514, Dec., 1956.

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